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THE RELATION OF METHODS OF DISPOSAL OF SEWAGE TO THE SPREAD OF PELLAGRA *

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INTRODUCTION

In analyzing the data collected in 1912 we were struck by the inequalities in the distribution of pellagra in the townships of the county in which our studies were undertaken. This rate ranged from no cases to 71 cases per ten thousand of population. A further analysis, based on the distribution of the population in rural, urban and mill-village communities showed that in rural communities the incidence rate was 16 per ten thousand of population; in the city of Spartanburg, exclusive of the mill-village section, it was 29 per ten thousand, while in the mill-village communities it averaged 104 per ten thousand.

One of the features of our epidemiological work in 1912 was the investigation of methods of disposal of human wastes. In certain sections of the city of Spartanburg a water-carriage system was in use. In the rural districts the white farmers usually had the unscreened surface privy. Privies were but seldom found on the premises of negro tenants on the farms. In the cotton-mill villages, about twenty-eight in number, in which pellagra prevailed much more extensively than elsewhere, two types of privy were in use. The usual type was an unscreened wooden outhouse where the excreta were deposited on the ground. In a few mill-villages the privy type was an unscreened wooden outhouse provided with metal containers for the reception of fecal matter. In some of the villages scavengers cleaned the privies at weekly intervals; in others at less frequent inter-

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vals or irregularly. These villages were laid out in streets, the dwelling-houses were but short distances apart and the privies necessarily in close proximity to the dwelling-houses. No effort was made to screen these privies; flies and other insects had free access to the collections of excreta.

In a series of 243 cases of pellagra investigated in 1912, the following methods of disposal were found to be in use.

In 5 per cent. (11 of the cases) a modern water-carriage system was used.
In 20 per cent. (51 of the cases) the unscreened wooden outhouses were equipped with metal receptacles.
In 60 per cent. (152 of the cases) the privy was an unscreened wooden outhouse, the feces being deposited on the ground.
In 12 per cent. (29 of the cases) there were no privies.

The average sanitary index of the privies used by these 243 pellagrins was 16 per cent., computed in accordance with the methods adopted by the Rockefeller Sanitary Commission. The existing sanitary conditions were summarized as follows:

The most insanitary condition found in the county is the absence of properly constructed privies. Outside of a part of the city of Spartanburg, which is supplied by a water-carriage sewage system, there is no effective provision in the county for the proper disposal of human excreta. A second striking insanitary condition is the almost complete absence of effective screening of dwellings. These two conditions present a situation highly favorable to the transmission of disease organisms eliminated in the excreta, both by direct contamination of food and persons and by insects. This situation is naturally aggravated in the mill villages and small towns by the greater congestion of houses.

As a result of these, as well as other observations, the members of the commission were impressed with the possibility that insanitary methods of disposal of human wastes might be an important factor in the spread of pellagra.

In the course of our investigations during 1913 it was determined that this feature should receive special attention. The principal point which we endeavored to ascertain was whether the endemic foci of the disease were more common in those communities and in those sections of cities in which the methods of disposal of human wastes were insanitary. In order to ascertain these facts we made a careful study of the exact distribution of the cases of pellagra, including a history of its distribution in the past. By personal visits to pellagrins and their relatives it has been possible for us to secure definite information as to the exact residence of pellagrins. We have endeavored to locate precisely all houses occupied by them from the inception of the disease up to the present time. The information relative to residence, as well as to other pertinent facts, has been transferred to our pellagra "house card," a copy of which we show. These "house cards"

have been filed by locality and from them we have constructed spot-maps showing the exact location of the cases of pellagra of which we have record.

HOUSE CARD

House No. *190.* Township, *Spartanburg. Whitney.*
Loation, *Whitney Mills No. 101.*

Pellagrous History No.	Date, *July, 1913.* First Erythema (Place, Date)
86. Here from *Jan. 22, 1912,* to *early in 1913.*	*July, 1911. Clifton No. 2. H. No. 191.*
87. Here from *Jan. 22, 1912,* to *early in 1913.*	*June, 1912. Here.*
88. Here from *Jan. 22, 1912,* to *early in 1913.*	*June, 1912. Here.*
89. Here from *Jan. 22, 1912,* to *early in 1913.*	*June, 1912. Here.*

Notes—*86* = *mother; 87* = *son; 88* = *daughter; 89* = *daughter.*
Apparent house of origin for Cases *Nos. 87, 88, 89.*
House: Construction—*Frame.* Screened, *no.*
Sanitary Condition—Good, poor, *fair.*
Water Supply—Well: *dug, with bucket. Deep.* Surface contamination, *no.*
Disposal of Excreta—Privy type: A, B, C, D, *E,* F. Distance from house, *twenty yards.*
Method of Ultimate Disposal—*Scavenger.*
General Sanitary Condition—*Poor.*

In all the mill-villages in Spartanburg County unscreened surface privies were in use and, in order that possible contrasts in the prevalence of pellagra might be shown, for the purpose of this study, it was necessary to extend our investigations to industrial communities elsewhere in the state in which water-carriage systems of sewage disposal had been installed. Through the state health authorities we learned that four cotton-mill villages in the state had adopted such methods of disposal. In two of these villages, one situated in Greenville, S. C., and the other in Union, S. C., the water-carriage sewer systems had been installed less than a year. The third was the Newry mill-village in Oconee County in the western part of the state, in which a water-carriage system of sewage disposal was installed about twenty years ago. The fourth village was the Republic mill-village in Chester County, situated in the northern part of the state, in which a water-carriage system was installed about three years ago. We have investigated the sanitary condition and prevalence of pellagra in the Newry mill-village and the Republic mill-village. As the water-carriage system of disposal had been in use in the other two villages for only a few months, their investigation was left to the future.

This study has enabled us, first, to compare the prevalence of pellagra in sewered and unsewered portions of the city of Spartanburg, and second, to make a similar comparison of two entirely sewered villages with a large number of villages where unscreened surface privies were in use.

THE SPREAD OF PELLAGRA IN THE CITY OF SPARTANBURG AND ITS RELATION TO VARIOUS METHODS OF DISPOSAL OF HUMAN WASTES

We have record of a total of 268 cases of pellagra in the city of Spartanburg (204 white and 64 colored). This includes not only the pellagrins living there in 1913 but also all known cases which have occurred. Of these 268 cases, 168 are known to have originated in the city.

Fig. 1.—Map of Spartanburg, S. C., showing plan of city.

Figure 1 is a reproduction of the plan of the city, the black portion in the center indicating the location of the business section. It will be noted that there are three mill-villages within and two just beyond the city limits. The largest cotton-mill is situated in the northwestern quadrant, the next largest in the northeastern, and the smallest in the southwestern quadrant.

Figure 2 shows the geographical distribution of pellagra in the city of Spartanburg together with the distribution of the sewer mains. It is clearly evident from this map that practically all the active foci of the disease were in the sections of the city in which unscreened surface privies were used. Two active foci of the disease existed in the southeastern quadrant of the city. One of these foci was in a sewered district but none of the pellagrous houses had sewer connections. The other was in a negro settlement and all the privies in this vicinity were of the unscreened surface type.

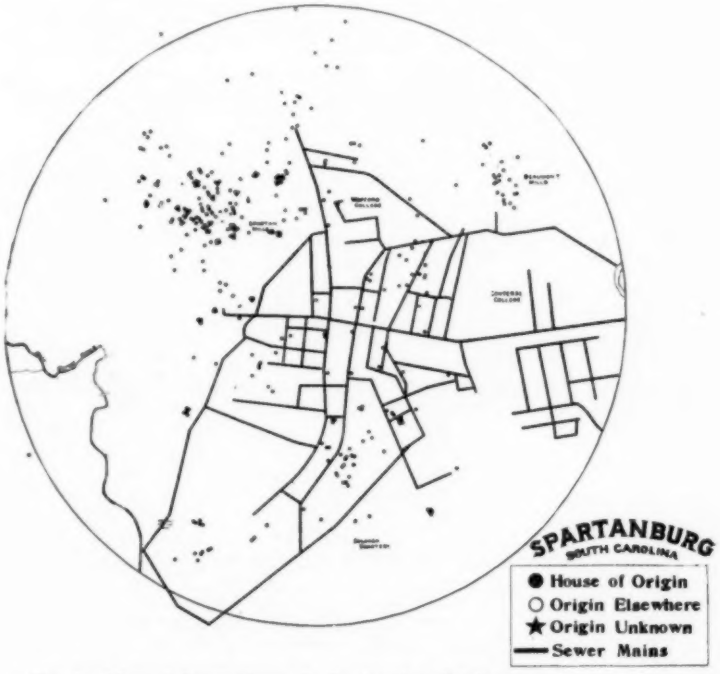

Fig. 2.—Map of Spartanburg, S. C., showing distribution of cases of pellagra in the city and distribution of sewer mains. Note that 168 of these cases originated in the city and that the largest number of cases occurred in the northwestern quadrant.

Of the total 268 cases of which we have record in the city of Spartanburg, we have investigated methods of disposal of excreta in 241 instances. In 230 cases, or 95 per cent. of the total investigated, the method of sewage disposal was the unscreened surface privy. In eleven instances, or 5 per cent. of the total, a water-carriage system of disposal was in use. A detailed examination of the records of these eleven cases has shown the following facts:

Patient 12 was a white woman, aged 40, married, whose residence had not changed since 1907. She contracted pellagra in 1911 and had mild recurrences in 1912 and 1913. She lived on one of the better residential streets; her circumstances were comfortable, and her only occupation was housework. The house was not screened. She gave no history of association with pellagrins, except visits to two persons suffering with pellagra. Our records, however, show that in a house immediately in rear of hers, Patient 496, a colored female, died of pellagra, July 12, 1910, and that during 1911, Patient 379, a colored female, lived directly across the street from her. The houses of these two colored pellagrins had the usual unscreened surface privies.

Patient 19, a white man, aged 20, contracted pellagra in the spring of 1911. His residence remained the same from 1905 to the fall of 1912. His home was in the best residential section of the city and the house was effectively screened. He was a college student and his circumstances were comfortable. His general health was good until the summer of 1909, when he contracted malaria in a saw-mill camp in South Carolina, near Augusta, Ga. Since that time his health has not been good. In 1910 he again spent five months (January to June) in a lumber-camp near the Georgia state line in South Carolina. This patient had severe recurrences during 1912 and 1913. No cases of pellagra have been located in the vicinity of his home in Spartanburg and there is no history of association with pellagrins.

Patient 24, a white man, aged 61, contracted pellagra in May, 1912. His residence had remained the same for several years. His home was situated in a good residential section but was not screened. He had been engaged in clerical work since 1881; his health had been good, and his circumstances appeared to be comfortable. He gave no history of association with pellagrins and we were not able to locate any cases in the vicinity of his residence. The disease recurred in 1913 and he died in the fall of 1913.

Patient 40, a white woman, aged 63, contracted pellagra in February, 1912. She had not changed residence for two years except for prolonged visits to relatives in South Carolina. Her home was situated in the business section of the city and, though it was screened, the screening was not effective. Two visits were made to this home by members of the commission. We found the screens raised, swarms of flies present and the general sanitary conditions very unsatisfactory. The patient's economic circumstances were poor and her occupation was housework. Patient 342, a white woman, who was a chronic pellagrin, lived with her during August, September and October, 1911. This patient (No. 40) died of pellagra, Aug. 10, 1912, having first shown symptoms in February, 1912.

Patient 57, a white woman, aged 43, first showed symptoms of pellagra on June 27, 1912. She lived in the best residential section of the city and had been living there since 1910. Her home was effectively screened and her husband well-to-do. She apparently had had some gastric disorder for a number of years. Her only occupation was the supervision of her housework. There was no history of association with pellagrins and no pellagrins lived in the immediate vicinity. There was no definite recurrence during 1913.

Patient 59, a white woman, aged 38, contracted pellagra in March, 1909, three months after confinement. Her home was in one of the best residential sections of the city and she had been living there since 1907. Her house was screened in part and her circumstances were those of comfort. There was no history of pellagra in her family and she gave no history of association with pellagrins. She had slight recurrences in 1910, 1911, 1912 and 1913.

Patient 208, a white man, aged 59, developed pellagra in December, 1909, and severe symptoms persisted until September, 1910. He had completely recovered from the attack in November, 1910, since which time his health had been good. The house of origin for this case was situated in one of the better residential sections and he lived there from 1907 to early in 1912. His circumstances were those of comfort and his health prior to the development of

pellagra had been good. No pellagrins have been located as living in the immediate vicinity of the house of origin for this case. For several years it had been the patient's custom to make visits from time to time to relatives in certain country districts in the county. One of his sisters died of pellagra in 1907 and another died of pellagra in 1910. Both were living in Spartanburg county and were well-to-do. His health has been excellent since November, 1910.

Patient 233, a white woman, married, contracted pellagra in May, 1910, in a house located in the best residential section of the city. She lived in this house from August, 1908, to March, 1911, and it was not screened. Her husband was well-to-do and she had enjoyed good health prior to the development of pellagra. Symptoms recurred in 1911, but there was no recurrence in 1912 and 1913. We have no record of pellagrins living in her immediate vicinity during 1909 and 1910. Her father-in-law (Case 321) died of pellagra in September, 1910, at his home in an unsewered portion of the city of Spartanburg and she had visited him there frequently during his illness.

Patient 426, a white woman, single, died of pellagra in 1902. Her father was well-to-do. Prior to the development of pellagra her health is said to have been good. She had been living in the same house for many years. As the condition was not recognized as pellagra until several years after her death the history is very incomplete. Evidence of association with other cases of pellagra is wholly lacking.

Patient 541, a white woman, aged 21, married, first showed erythema in April, 1913, though she gave history of ill health since November, 1912. She had lived since 1909 in a good residential section and the house was screened in part. Her circumstances were those of comfort and her health had been good prior to November, 1912. The nearest case of pellagra was a white man, Patient 5, who contracted pellagra in 1911 and died of it in 1912 in a house directly across the street. His house was provided with an unscreened surface privy. This woman, Patient 541, made a visit of three weeks' duration, during the summer of 1912, to relatives in a southern state on the gulf coast where surface privies were in use. There was no history of association with pellagrins.

Patient 755, a white man, aged 32, druggist, contracted pellagra in the spring of 1913 and died of it in August, 1913. During 1913 he lived in the best residential section of the city and was well-to-do. The history of this case is very incomplete and we have no data concerning association with pellagrins.

Of the eleven patients, three (Cases 12, 233 and 541) gave a history of living or visiting in the same house or next door to pellagrins using surface privies; another (Case 40) lived under very insanitary conditions in the same house with a pellagrin; and a sixth (Case 208) had two sisters who were pellagrins, one dying before he developed the disease and the other dying the following year. Two, Patients 24 and 755, were men engaged in occupations bringing them constantly into contact with the general public. In the other four cases, (Nos. 19, 57, 59 and 426) we have been unable to learn of any relationship whatever to antecedent pellagra.

THE SPREAD OF PELLAGRA IN UNSEWERED MILL-VILLAGES IN SPARTANBURG COUNTY

Our records show that pellagra occurred and has originated in all the mill-villages in Spartanburg County. In all these villages unscreened privies were in use. In some, the fecal material was col-

lected in pails; in the majority, however, it was deposited on the ground. Many of these mills were situated but a few miles distant from one another and for a number of reasons there was a tendency for certain elements of their population to move, with great frequency, from one mill to another. This element of the population—generally termed "floating"—varied from about 15 per cent. to even more than 33 per cent. Cases of pellagra commonly occurred in this floating element and frequently it was necessary for us to trace pellagrins from mill-village to mill-village before finally locating them.

Six of these villages were selected for intensive studies and by house-to-house visitations all existing cases of pellagra were accurately located. The incidence rate for 1912 and 1913 was higher in

Fig. 3.—Distribution of pellagra in mill-village "W," Spartanburg County. Unscreened surface privies are shown as small blocks in the rear of dwelling-houses. Note that twenty cases of pellagra have originated in this village.

some villages than in others, but incident cases occurred in every village during 1912 and 1913. It was observed that in several of these villages incident cases of pellagra would be quite numerous one season and relatively few the next, or *vice versa*.

Spot-maps have been constructed of these mill-villages showing the distribution of pellagra. Figure 3 is a reproduction of the plan of village *"W"* showing the distribution of the disease, and this is a fair example of conditions in all these villages. It will be noted from this map that at least twenty cases of pellagra have originated in this village.

HISTORY AND SPREAD OF PELLAGRA IN MILL-VILLAGES IN WHICH WATER-CARRIAGE SYSTEMS OF DISPOSAL OF SEWAGE HAVE BEEN INSTALLED

Newry Mill-Village

This village is located in Oconee County in the northwestern part of South Carolina. It was built about twenty years ago, its first president being Captain Courtenay of Charleston. Captain Courtenay installed a water-carriage system of sewage disposal before the mill-village dwellings were occupied and this system has been continuously in use to the present time. The closets have been grouped (from four to eight in each group) in detached houses convenient to a group of dwelling-houses, rather than as individual closets in each dwelling-house. One of these privies has been assigned to each dwelling and the tenant held responsible for its proper care. The annual cost for repairs and upkeep has amounted to but little. The total population was 750. The operatives employed in the mill were recruited from the same sections and from the same elements of the population, as were operatives in mills elsewhere in the state. They were accustomed to eat the same foods as were eaten by the inhabitants of other mill-villages throughout the state. The company store was selling about a bushel of shipped (western) corn-meal to each family per month. The only respect in which their dietary habits possibly differed from those of some of the mill-villages in the state, lay in the fact that fresh meat could be obtained throughout the year from a local market. In some of the mill-villages in Spartanburg County fresh meat was not on sale in the village during the hot summer months. In others, however, where pellagra prevailed extensively, fresh meat could be obtained throughout the year from the mill-village market.

The Newry village is almost surrounded by permanent streams, and the eggs and larvae of *Simulium* were observed in abundance. The only demonstrable difference between this mill-village and (with three exceptions) those elsewhere in the state lay in the fact that a water-carriage system of sewage disposal was used there, while the method employed elsewhere was the unscreened surface or pail privy. With these facts in mind it is of interest to study the history of pellagra in this village.

In August, 1911, a woman showing active pellagrous skin lesions came into the village from Georgia. She departed the same day on the advice of the local physician and has since died.

In the spring of 1908, a family which had been resident in the village for several years, purchased a home near the railway (at Courtenay Station) about one mile away. They lived there until December, 1911. A woman with pellagra resided next door during the period of their residence at Courtenay Station. In June, 1909, the mother (Case 2064) contracted pellagra. In December, 1911,

they returned to the Newry mill-village and were still there in October, 1913. The family consisted of six adults and one child. No other case of pellagra was observed in the family and this one case had recurrences in 1910, 1911, 1912 and 1913.

Another woman (Case 2060), one of the four patients now resident in the village, gave a rather indefinite history of pellagrous symptoms as far back as 1910. The family had been extremely migratory and it was difficult to determine with certainty exactly where and when the disease developed. She first lived in the village for two months in the winter of 1910 and it is possible that she was at that time pellagrous. The first positive history of the disease began in the spring of 1912, when a frank erythematous rash appeared. At that time she was living on a farm some ten miles north of the village. She returned to Newry in November, 1912, and lived there until the last of February, 1913. She was then away until June, 1913, when she returned to the village and was still there in September, 1913.

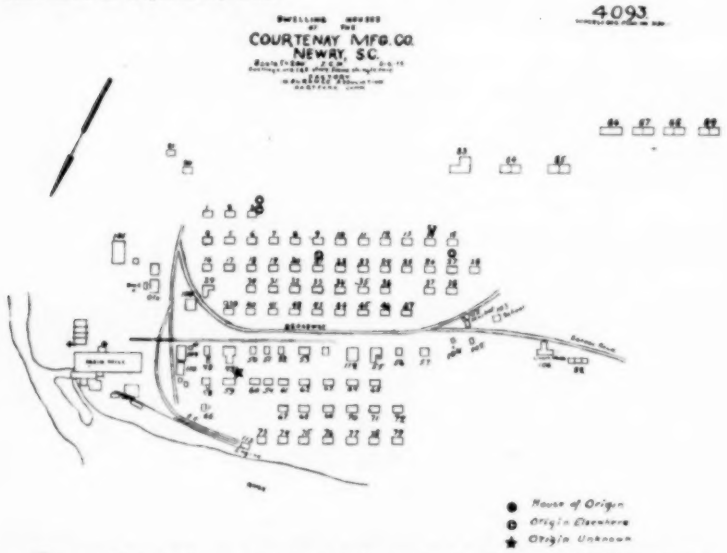

Fig. 4.—Distribution of cases of pellagra in the Newry mill-village having a water-carriage system for disposal of sewage. Note that all patients with one possible exception contracted pellagra before moving into the village.

Patient 2061, who had been a pellagrin since 1910 and had had a recurrence each succeeding year, first moved to the village in November, 1912, and still lived there in September, 1913. Her 10-year-old son (Case 2062) had pellagra, but he likewise developed the disease early in 1912 before coming to the village.

Case 2063, that of a young woman who died of pellagra in Newry, Aug. 17, 1913, offers the only instance of possible origin in this mill-village, inasmuch as she moved there late in the fall of 1912 (exact date not known) and apparently did not have any erythema prior to Aug. 3, 1913, two weeks before death. She was under treatment by the local physician for persistent diarrhea from June 6, 1913, and gave a history of stomatitis, diarrhea and general poor health the previous year, while living at another village in a house within a few doors of at least two other cases of pellagra. It seems highly probable that she was a pellagrin in 1912 before coming to Newry.

The history of pellagra in this village may be summarized by saying that five pellagrous patients have been observed, all of whom, with one possible exception, were suffering with pellagra on arrival in the village. No case of pellagra clearly originating in the village has been found. Figure 4 indicates the distribution of pellagra at the Newry mill-village.

As a control study we investigated the prevalence of pellagra in a mill-village on the outskirts of Seneca, S. C., about four miles distant from Newry mill. The methods of disposal of human wastes in this village were exactly similar to those observed in mill-villages in Spartanburg County (unscreened surface privies). We were shown active cases of pellagra originating in this village. The history of pellagra in this village as given us by the local practitioners indicated that it had prevailed here to much the same extent as in the mill-villages in Spartanburg County.

Oconee County had not so large a number of cotton-mills as Spartanburg County, nor were the mills in such close proximity one to another. For this reason the "floating" or transient population was appreciably smaller.

Republic Mill

This mill is situated at Great Falls, Chester County, in the north central part of South Carolina. It was built in 1910 and was put into operation in June of that year. There were ninety-two houses in the village and its population was between 475 and 500. Before building the village, Mr. R. S. Mebane, president of the mill, made a special study of the problem of the proper sanitation of mill-villages, especially with reference to the water-supply and sewerage. In building the village he constructed a complete sewer system, connected with every house, and placed in each house a kitchen sink and flush closet. The system differed from that at Newry Mill in that the closets were placed in the houses instead of being grouped outside. This mill-village was visited for two days in September, 1913, and as complete a study made of the pellagra situation as was possible in that time. Dr. J. B. McKeown, the resident physician, kindly gave practically the entire two days to assist in the inquiry. Notes were secured of six cases of pellagra concerned in the history of the village during the three years of its existence.

The first patient, a woman, aged 30, had lived in the village only four months. She was at about term with her fourth child. She had no erythema when seen and said she had never noticed any. When seen by us she had a very bad stomatitis and glossitis and had suffered with persistent diarrhea for the past nine months. She had lost considerable weight and had suffered recently with severe burning of feet. While, in the absence of any skin manifestation, it was not considered possible to make an absolutely positive diagnosis, we agreed

with Dr. McKeown in considering hers a very probable case of pellagra. There was no question, however, but that her symptoms antedated her coming to Republic Mill.

A second case, not now in the village, was reported by Dr. McKeown as having moved there in January, 1913. The patient first came to his attention in April, 1913, when she was confined. About three weeks later he was again called and found her with all the symptoms of an active attack of pellagra—diarrhea, nervous symptoms, bad stomatitis, and a symmetrical erythema on the backs of her hands. She left the village the following June. In November we received a letter from Dr. L. S. Hay of Rock Hill, a former physician of the case, saying that she had been a pellagrin under his care the previous year before coming to Republic Mill.

The third patient was a woman who had been a pellagrin since the spring of 1909 and had lived in Republic Mill for the past two years. She had had no active symptoms of the disease during the period of her residence in the village.

The fourth case was that of a boy aged 8, who came to the village in March, 1913. When seen he showed no evidence of the disease except a symmetrical scaliness and pigmentation of the backs of the hands. In the spring of 1913 he had an erythema of hands and feet and an attack of sore mouth. He was seen by Dr. McKeown at that time and the case diagnosed as pellagra. According to his father's statement he had suffered an exactly similar attack, though rather more severe, in March of the previous year (1912) before coming to Republic.

The fifth case was that of a boy, aged 6, who, according to Dr. McKeown's statement, presented a typical erythematous rash of both hands and feet and was suffering from diarrhea and sore mouth and tongue during the summer of 1912. The erythema had appeared in June, 1912, and he had come to the village the preceding January. His mother stated that he had a somewhat similar rash the previous year (1911) before coming to Republic, which she thought was "poison oak." She said that she "broke out" the same way on her hands, face and neck about six years ago and that her mouth got sore. She also stated that her father was said to have died of pellagra. The woman was of a very low order of intelligence and her statements were not considered very reliable. A diagnosis in her case was not possible and the time of appearance of the boy's first symptoms could not be determined positively. The case must be considered as possibly originating at Republic Mill, but there was a fair probability that the boy was pellagrous prior to coming to the village.

The sixth patient, a colored woman, aged 35, did not live in the village proper, but in a cabin about one fourth of a mile distant. This was a typical case, but the patient had been living there only a short while and her symptoms clearly antedated her present residence.

Of the total six cases which could be discovered in the three years history of the village, only one could possibly have arisen there and in that case the evidence seemed to point to probable origin elsewhere. Figure 5 shows the distribution of pellagra in this village. Two of the cases cited above are not shown on this map because the patients lived beyond the limits of the village.

One significant fact in these two villages was the difficulty encountered in finding cases of pellagra even by careful search, whereas in all other villages studied, a few moments' inquiry was all that was necessary to locate many cases of pellagra, well known to the population at large.

The second striking feature, of course, was that, with two doubtful exceptions, each of the eleven patients affected with the disease who could be found in these two water-sewered villages had been pellagrins prior to coming to the respective villages. It appears, therefore, that while cases of pellagra had been introduced into these villages from time to time during their history of twenty and of three years, respectively, no case of the disease could be shown definitely to have originated in these villages and only two could possibly have done so.

With reference to Republic Mill, the point arises whether three years is not perhaps too short a time for pellagra to show itself in a newly constructed village. That this is not true is demonstrated in the case of a mill-village in Spartanburg County which was built in 1911 and went into operation in April, 1912. During the following year five known cases of pellagra moved into the village. Two chil-

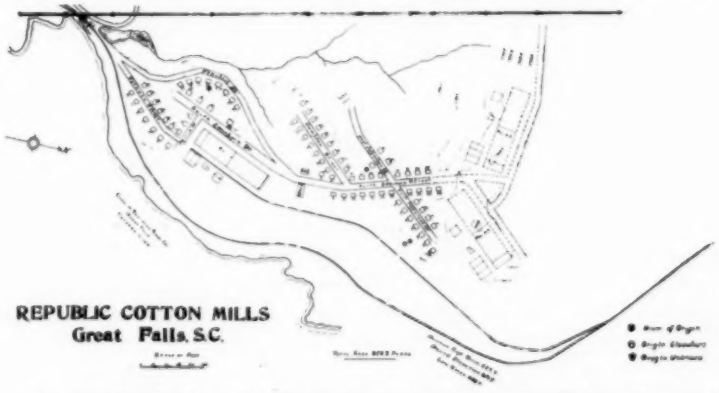

Fig. 5.—Distribution of pellagra in the Republic mill-village. Note that with one possible exception all pellagrins contracted the disease elsewhere and moved into the village with pellagra.

dren (Cases 546 and 585) who in July, 1912, moved into the house next door to one of these imported cases, developed typical pellagrous symptoms in May and June, respectively, the following year (1913). There were very clear histories of the absence of any previous manifestations of the disease. A third patient (No. 745), a boy of 7 years, developed pellagra in March, 1913. There was no history of a previous attack. The immediate connection with a previous case of pellagra appeared to be the boy's grandfather, who was a pellagrin and had visited the family during the previous winter. The development of these three cases within little over a year after the newly built village was first occupied would argue strongly that the apparent freedom of Republic mill-village from pellagra cannot be explained

by the assumption that a period of three years is not sufficient time for the disease to manifest itself in a new locality.

Each of the villages here cited is still under observation, and it is our intention to follow them for at least another year, both in order to determine the presence or absence of pellagra and to ascertain, if possible, any factors other than the presence of water-carriage systems of sewage disposal which may differentiate them from those villages showing a high prevalence of pellagra.

THE SPREAD OF PELLAGRA IN UNSEWERED RURAL COMMUNITIES

We have referred to inequalities in the distribution of pellagra in Spartanburg County and have cited the fact that our records showed an incidence rate of sixteen per ten thousand of population in rural communities, against 104 per ten thousand in mill-village communities.

So far as disposal of excreta is concerned the only important difference between these two elements of the population was the fact that unscreened surface privies were always found in mill-village communities, while in rural communities, not infrequently, there was no visible method of disposal. The absence of privies applied more particularly to the colored tenant farmers. Where privies were found in rural communities they were practically always of the unscreened surface type.

The most important contrast between rural and mill-village communities appears to be density and congestion of population. There were isolated instances in rural communities in Spartanburg County where foci of pellagra appeared to exist and we made an extensive study of one such district. In this farming district covering an area 2 miles square, there was a total population of approximately 260 persons, 100 white and 160 colored. We secured records of a total of eleven cases of pellagra occurring in this population since 1906, four cases in the white population and seven cases in the colored. The incidence rate for pellagra in this rural community was 423 per ten thousand of population while the incidence rate for the rural population of the county as a whole was only 16 per ten thousand of population. In this district a history of close association between previously existing and new cases was demonstrable. There was a general tendency for active foci of pellagra in rural communities to occur in townships in which mill-villages were located and the focus mentioned above occurred within about 2 miles of a mill-village community where pellagra was endemic.

The methods of disposal of human wastes in the county in which our studies were undertaken are typical of those in use throughout the southern states where pellagra prevails so extensively. Recent sta-

tistical reports of the Rockefeller Sanitary Commission[1] indicate quite clearly the sanitary conditions existing in the Southern states at the present time. Of 189,510 homes inspected in rural communities it was found that 95,735 had no privy. The sanitary index for the total number investigated was only 5.8 per cent.

THE PREVALENCE OF PELLAGRA IN INSTITUTIONS WITH WATER-CARRIAGE METHODS OF DISPOSAL OF SEWAGE

The prevalence of pellagra in institutions for the insane, having water-carriage systems of disposal of sewage, is of particular importance in the discussion of any possible relationship between the spread of pellagra and methods of disposal of human excreta. We have been unable to obtain any definite information relative to the actual incidence rate of pellagra in asylums in the southern states. The disease is endemic in these states and cases of pellagrous insanity are being admitted to these institutions at frequent intervals. Very frequently symptoms of the disease are observed within a short time after admission and even though there be no suspicion or definite evidence of the disease on admission, it is impossible, from the histories obtainable, to arrive at any definite conclusion as to where the person contracted pellagra. It is a fact, however, that, not infrequently, patients show active symptoms of the disease for the first time, several years after commitment.

So far as we have been able to ascertain, there is probably only one institution for the insane in this country in which a severe epidemic of pellagra has occurred and in which there appeared to be no question that practically all the patients contracted the disease in the institution. We refer to an epidemic of pellagra at the Peoria State Hospital at Peoria, Ill.[2] Two of the members of this commission took part in an investigation of this epidemic and it was studied most thoroughly by the Pellagra Commission of the State of Illinois. Dr. George A. Zeller, superintendent of this institution, recalls very distinctly that cases of pellagra occurred in the Peoria Hospital as early as 1907 and has records of such cases, though they were not, at that time, recognized as such. In 1909, however, there was a sharp outbreak of pellagra in the institution involving more than 8 per cent. of the inmates (177 cases). Table 1 shows the total number of incident cases for each year from 1909 to 1913 inclusive. All cases for 1909 are tabulated as incident cases because accurate records were not available prior to that time. The mortality rates in

1. Fourth Annual Report, The Rockefeller Sanitary Commission.

2. Report of the Pellagra Commission of the State of Illinois, November, 1911, Springfield, Ill., 1912.

this epidemic were very high, particularly so during the year 1909 (50 per cent.). The severe outbreak of pellagra in 1909, with the sharp decline in succeeding years, is most interesting.

TABLE 1.—INCIDENT CASES OF PELLAGRA AT THE PEORIA STATE HOSPITAL, PEORIA, ILL.

Year	1909	1910	1911	1912	1913	1914 (to March 15)
Cases	177	67	14	0	0	0

The institution had a most excellent water-carriage system of disposal of sewage and it is not possible to attribute the 1909 epidemic

TABLE 2.—PELLAGRA ARISING IN THE WARDS OF THE PEORIA STATE HOSPITAL

Ward	Type of Patient	Habits*	Sex†	Population	No. of Cases of Pellagra	Incidence Per Cent.
Infirmary *A*	Infirm chronic...	±	♀	60	10	16.6
1 *A*	Staff house.....	....	....	....	....	....
2 *A*	Chronic	±	♀	50	7	14.0
3 *A*	Demented	—	♀	62	19	30.6
4 *A*	Epileptic	+	♀	60	7	11.7
5 *A*	Acute and chronic	+	♀	52	2	4.0
Infirmary *B*	Infirm chronic...	±	♂	60	3	5.0
1 *B*	Acute and chronic	+	♂	52	2	4.0
2 *B*	Demented	—	♂	52	13	25.0
3 *B*	Demented	—	♂	62	4	6.4
4 *B*	Epileptic	+	♂	58	8	13.8
1 *C*	Demented workers	+	♂	110	8	7.3
2 *C*	Demented	±	♂	110	9	8.2
3 *C*	Demented	±	♂	110	8	7.3
4 *C*	Irritable dements	+	♂	110	7	6.4
5 *C*	Irritable dements	±	♀	110	14	12.8
6 *C*	Irritable dements	+	♀	110	7	6.4
7 *C*	Feeble dements...	±	♀	110	6	5.5
8 *C*	Infirm old	+	♀	110	23	20.8
South dormitory..	Quiet workers....	+	♀	...	2	
Tent Col. *B*.....	Tuberculous	±	♀	57	12	21.0
Tent Col. *C*.....	Tuberculous	±	♂	57	5	8.8
Supply ward	Workers	+	♂	140	4	2.9
Domestic ward....	Workers	+	♀	64	1	1.5

*The sign + indicates that patients are all cleanly in habits; ± indicates that some are cleanly but many are not; — indicates that all patients are uncleanly. In this column ♂ stands for male and ♀ for female.

to improper methods of disposal of human excreta. It is to be remembered, however, that in many infectious diseases of intestinal origin, dependent mainly for their spread on faulty methods of disposal of human excreta, intimate association and contact may also be important factors. With this in mind, there are some suggestive facts which may be cited in connection with this epidemic.

The wards of this institution were constructed on the pavilion plan. Twelve of the pavilions had capacity for 60 patients. Eight pavilions housed 110 patients each; the supply ward had 140 patients and the domestic ward, 64. In assigning patients to wards an effort was made to distribute them according to cleanliness of habits. Through the courtesy of Dr. H. D. Singer, director of the Illinois Psychopathic Institute, Dr. George A. Zeller, member of the State Board of Administration and Dr. E. Z. Levitin of the Medical Staff of the Peoria State Hospital, we have secured information[3] covering the distribution of 181 cases of pellagra arising in the early stage of the epidemic at Peoria. Table 2 shows the distribution of cases in the different wards and each case has been charted in the ward of apparent origin.

It will be noted from this table that, except for Wards 8 *C* and 3 *B*, there was a distinctly greater tendency for pellagra to spread in wards housing untidy patients (3 *A* and 2 *B*) than in those housing patients of cleanly habits. It is also evident that the patients in 8 *C*, which shows a high rate of incidence, were of advanced age and infirm.

Omitting the two cases which occurred in the south dormitory, for which population figures are not at hand, there remain 179 pellagrins. The distribution of these cases according to cleanliness of habits is shown in Table 3.

TABLE 3.—Distribution of Pellagra in Wards of the Peoria State Hospital According to Cleanliness of Habits

Character of Inmates	Population	No. of Pellagrins	Incidence Per Cent.
All cleanly habits	866	69	8.0
Mixed: some cleanly habits and many uncleanly	724	74	10.2
All uncleanly habits	176	36	20.5
Total	1,766	179	10.1

The incidence rate of pellagra in the untidy wards was 20.5 per cent., two and a half times greater than in wards housing patients with cleanly habits, in which it was 8 per cent.

The food for the inmates was distributed from a central kitchen. One of the early and severe cases in the institution was that of a woman employed in the central kitchen. She had a very severe attack of pellagra during the summer of 1908 while working in the kitchen and her symptoms became so severe as to necessitate her admission to the hospital.

3. Personal communication, March, 1914.

In August, 1909, Dr. Zeller, the superintendent of the institution, decided to establish in the hospital proper, male and female pellagra wards. In the fall of 1909 practically all the pellagrins in the institution were transferred to these wards, a graduate nurse was assigned to each ward and daily notes were made on the cases. During the summer of 1910, the pellagrins were still segregated and as new cases of the disease arose they were transferred to hospital. Dr. E. Z. Levitin of the hospital staff informed us recently (March, 1914)[4] that segregation was practiced until the fall of 1911, when the patients were so few that the practice was discontinued. He states further that, except for one chronic pellagrin, there are at the present time (March, 1914) no active cases of pellagra in the institution. This segregation and practical isolation of pellagrins may possibly have been a factor in the remarkably rapid disappearance of pellagra from this institution. The death-rate among pellagrins in this institution was also remarkably high, thus diminishing the number of hypothetical sources of infection.

DISCUSSION

This study shows inequalities in the geographical distribution of pellagra in Spartanburg County. Furthermore, in those communities and elements of the population in which methods of disposal of human excreta were similar, its distribution was still unequal. In the section in which our studies were undertaken, congestion of population, general sanitary conditions being equal, appeared to be an important factor in producing higher incidence rates. Thus we found that, where the population was congested in Spartanburg County, as was the case in mill-village communities, the pellagra morbidity per ten thousand of population was six and a half times greater than in rural communities where the population was sparse. (Rural rate per ten thousand was 16, mill-village rate per ten thousand was 104.)

In the city of Spartanburg there was a distinct tendency for the endemic foci of the disease to be confined to those sections of the city in which unscreened surface privies were in use. Information given us by physicians practicing elsewhere in the South indicates that the distribution of the disease, in at least some other southern cities, coincides, so far as methods of sewage disposal are concerned, with its distribution in the city of Spartanburg. It is our intention, during 1914, to study the distribution of the disease in a number of cities and industrial communities, with particular reference to methods of disposal of sewage.

4. Personal communication.

Fig. 6.—Type of unscreened trough privy formerly in use in Spartan mill-village.

Fig. 7.—General view of unscreened trough privies formerly in use in Spartan mill-village.

Pellagra prevailed and originated in all the mill-village communities in Spartanburg County and in all these communities the methods of disposal of excreta were unscreened surface privies. We investigated the history of pellagra in two mill villages elsewhere in the state in which the only striking contrast was the fact that a complete water-carriage system of disposal of sewage had been installed. In these

Fig. 8.—Type of water-closet recently installed in Spartan mill-village.

villages we found that, notwithstanding the fact that pellagrins moved in from time to time, thus far, there had been no tendency for pellagra to originate or to spread in these communities. These observations appear to us to be somewhat striking and strongly suggest the possibility of a direct relationship between the spread of pellagra and faulty methods of disposal of human excreta.

There is a wide-spread movement under way at the present time in the southern states toward the improvement of methods of disposal of human excreta. Many towns and cities as well as industrial communities in which pellagra is endemic are either improving their types of surface privies or putting in modern water-carriage systems of disposal. It is in such communities that most important information can be obtained, either confirming or refuting these observations. Superficial studies and general impressions will not suffice. If any information of value is to result, the local health officers and physicians in communities, in which improved methods of disposal are being installed, must necessarily know the history of the prevalence and distribution of pellagra prior to the installation of improved methods.

Fig. 9.—Rear view of a row of houses showing type of construction adopted in installation of water-carriage system of disposal of sewage in Spartan mill-village. The closet is on the back porch.

They must also necessarily keep accurate records, for at least three or four years, of the prevalence of the disease subsequent to the installation of improved sanitary methods.

One community exists in Spartanburg in which a water-carriage system of disposal has been substituted for unscreened surface privies. Reference to Figure 2 (the distribution of pellagra in the city of Spartanburg and its relation to methods of disposal of sewage) shows that the disease has prevailed most extensively in the northwestern quadrant of the city. In this quadrant is located one of the largest cotton-mills in the county. About 300 of the dwelling houses in this section are the property of this mill, and during the summer of 1913 the president of the mill, Mr. W. S. Montgomery, decided to install individual water-closets in each dwelling. Up to the present, pel-

lagra has been excessively prevalent in this section and the method of disposal of human wastes has been the unscreened trough system (Figs 6 and 7). The installation of a water-carriage system was begun in the fall of 1913 and is being pushed to completion. On Feb. 1, 1914, 123 installations had been completed and connected with the sewer mains. The type of construction adopted is shown in Figures 8 and 9. A special non-freezing type of closet has been installed, as the fixtures are exposed to sudden and sharp changes in temperature.

We have studied the prevalence of pellagra in this village during 1912 and 1913 and each case has been carefully located. We know that at least eighty cases of pellagra have originated in the northwestern section of the city during the past six years. It is our intention to observe carefully the behavior of the disease with respect to the development of new cases during 1914 and for two or three years thereafter.

In presenting these facts at this time, we hope that similar studies may be undertaken in communities elsewhere in the Southern states where pellagra is endemic and where contrasts in methods of disposal of human excreta present themselves.

SUMMARY

1. Pellagra morbidity was higher in congested communities using surface privies than in more sparsely settled districts in which similar methods for the disposal of excreta were employed.

2. In the city of Spartanburg the endemic foci of pellagra were located in the districts in which surface privies were in use.

3. In cotton-mill villages equipped with surface privies pellagra was found to be endemic and new cases of the disease arose there year after year.

4. In two cotton-mill villages completely equipped with water-carriage systems of sewage disposal it was impossible to find cases of pellagra which had certainly originated there, although some cases which had originated elsewhere were present.

5. There is some evidence that pellagra spreads in hospitals for the insane more readily in the wards housing untidy patients.

6. This study indicates that methods of disposal of human wastes may prove to be a determining factor in the spread of pellagra in certain communities and it suggests a possible method of prophylaxis, which is now being tested in a practical way.

Twentieth Street and Second Avenue.

NOTES ON A NORMAL, PRESYSTOLIC SOUND*

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BALTIMORE

In the course of some work recently undertaken in Dr. Thayer's service to localize the third heart-sound by the use of simultaneous tracings, a remarkably constant, presystolic sound-representation was observed on the electrophonogram; and its description will be the effort of this paper. The technic employed, the value of the Einthoven electrophonograph, and some of the factors concerned in the audibility of cardiac sounds have been previously discussed;[1] but attention may be recalled to the constancy and reliability of apex-tracings obtained in the left decubitus, and to the localization of the first sound by the foot of the ventricular rise of the apex cardiogram.

In a reconsideration of the tracings of sixteen normal schoolboys, it may be said that the pulse-rate varied from 65 to 100, diastasis[2] ranged from 0.12 to 0.50 second in the series, and from 0.21 to 0.39 second in an individual case, as opposed to a fairly constant systole and diastole, not only for the individual, but for the series.

Eleven of the apex-tracings showed definite auricular waves; these were in no way to be confounded with the wavelet sometimes seen on the anacrotic limb of the apex-tracing that marks the presphygmic period — the time between the onset of ventricular systole and the expulsion of blood into the aorta. The distance from the beginning and summit of the auricular wave is shown for the individual cases elsewhere (see Table); here it is sufficient to say that the beginnings of ventricular and auricular systole are separated by about 0.09 of a second, while the summit of the elevation associated with auricular systole follows its onset by closely 0.04 of a second.

Eleven of the phonograms showed a short presystolic sound-wave. Three of these were in cases in which no auricular waves were shown, while three boys, with auricular representation on the apex curves, showed no presystolic wave on their phonograms. This lack of agreement speaks strongly against simple pressure phenomena as being responsible for the phonographic curves. The presystolic sound begins, on an average, 0.07 of a second before the appearance of the first sound and at varying intervals after the preceding third and second sounds, depending on the inconstant diastasis. It is repre-

* Submitted for publication, June 10, 1914.

1. In a communication to appear shortly in Heart.
2. Henderson, Yandell: Am. Jour. Physiol., 1906, xvi, 325.

sented by a wave which, in most instances, shows displacement in but one direction and is probably, therefore, exposed to marked damping at the source. The wave is of a duration of closely 0.04 of a second, making the sound of a frequency, roughly, in the vicinity of 25 vibrations per second; and thus, in these cases, below the limits of human audibility. The amplitude averages about one-eighth the amplitude of the first sound, though it varies from one-fifteenth to one-fourth. In some cases, its corresponding galvanometric oscillation was greater than that of the third sound, which in several cases was

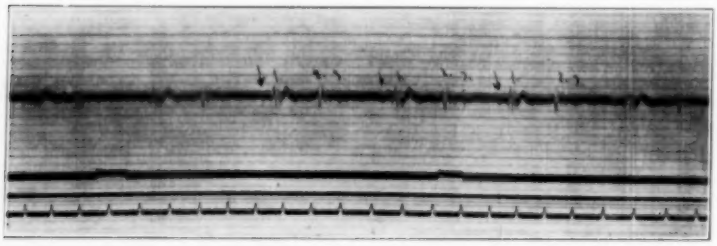

Fig. 1.—Electrophonogram of C. C., showing a definite presystolic and third sound. This and the following electrophonograms were taken with patient lying on back, and with varying strengths of primary circuit.

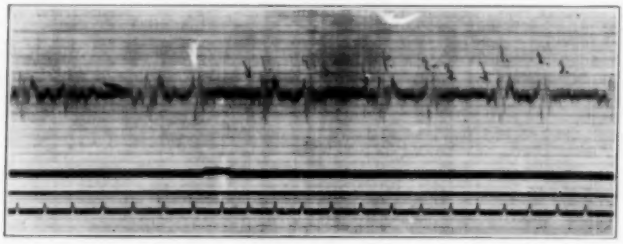

Fig. 2.—Electrophonogram of C. C., showing definite presystolic and third sounds. Arrows point to presystolic sounds.

clearly marked out in the same cardiac cycle. On the phonograms taken to show the greater amplitude of the third sound following increased venous pressure, as after elevation of the limbs, moderate exercise, etc., the presystolic sound shows similar accentuation.

Attention has been called to the danger of drawing absolute conclusions from these phonographic waves; they do not represent true sound-waves, but their transformation into electrical energy. It seems fair, however, to make these comparative statements which afford a mental concept as to the duration, position, and pitch of this sound.

There is, then, in many normal boys a presystolic sound that is generally below the limits of human audibility, and which occurs

about 0.02 of a second after the beginning of auricular contraction. Further description would involve the introduction of pathologic cases and would necessitate a discussion of the presystolic gallop—factors not to be undertaken in this description of a normal phenomenon.

It is interesting to endeavor to put forth some hypothesis as to the etiology of this sound—a hypothesis which, of course, must be substantiated by the known facts, and which must also be adaptable to pathologic conditions. In a normal cardiac cycle, the ventricle is nearly empty of blood at the end of systole; in 0.03 of a second after the closure of the aortic and pulmonic valves, the auriculoventricular

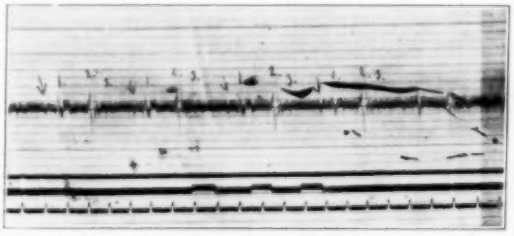

Fig. 3.—Electrophonogram of C. P., showing definite presystolic and third sound. Arrow points to presystolic sound.

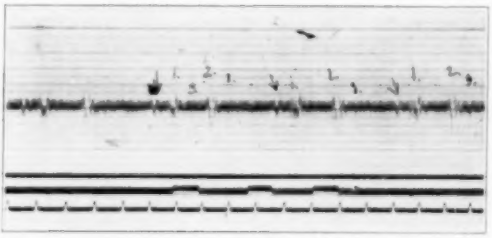

Fig. 4.—Electrophonogram of C. P., showing well-marked presystolic sound with a definite third.

valves open to allow the active period of ventricular filling—diastole. During this time, blood flows into the ventricle to an amount and to a resultant ventricular tension, depending first on the pressure of the blood dammed back into the auricles and veins by the preceding systole, secondly, on the tone of the ventricle, and thirdly on outside factors. Of outside factors, gravity is an example; for with the patient on his left side more blood is going to flow in because the tonicity of the ventricles must withstand an additional factor besides venous pressure —the force of gravity. The blood, then, flows in until there is a definite tension of the ventricular walls—a condition which is associated with the approximation of the auriculoventricular valves. The

ventricles are pretty well shut off from the auricles unless there is a very high, and rapidly increasing venous pressure, when the ventricles may be still further slowly distended by a small amount of blood oozing through the auriculoventricular apertures. As the ventricles rapidly distend, they may suddenly become taut, because of their tone, and there would, of necessity, be vibrations of the walls and thereby sound production. Were the ventricles distended with air a louder sound would be expected, but marked damping occurs with the particular type of fluid contact. With the onset of auricular contraction, more blood is thrown into the ventricles, whose walls become correspondingly more taut. At the same time, the whole floor of the auricles strikes against the distended, elastic bag, producing conditions favorable for sound formation. With the onset of systole, tension of the papillary system and the contractions of the ventricular walls on the contained fluid might produce vibrations of the stretched

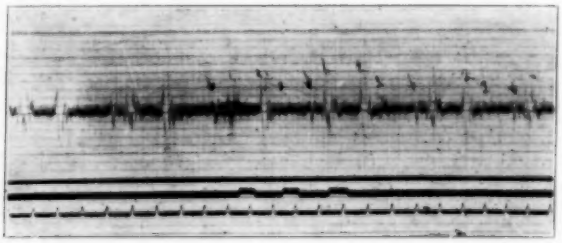

Fig. 5.—Electrophonogram of C. P., showing an unusually definite presystolic sound with third sound. Arrow points to presystolic sound.

tissue. During systole, as the ventricles contract steadily, the sudden impulse would be lost and the tissue itself would be shortened. So that the conditions favorable for sound would appear only in very early systole. At the end of systole there is no stretch of the walls —they are relaxed—so until they are made taut by blood distention there would be no expectation of sound production. This conception of muscle vibration has nothing to do with the valvular elements of the heart-sounds, elements which are so definitely the most important factors in their production. But it might explain the so-called "muscular element" of the first sound which is so hard to understand. The possibility of the vibration of a stretched and suspended elastic substance when acted on by an outside force offers a hypothetical explanation of the presystolic sound. That such vibrations may be associated with the valvular element of the first and third sound has suggested experimental investigation that is being undertaken.

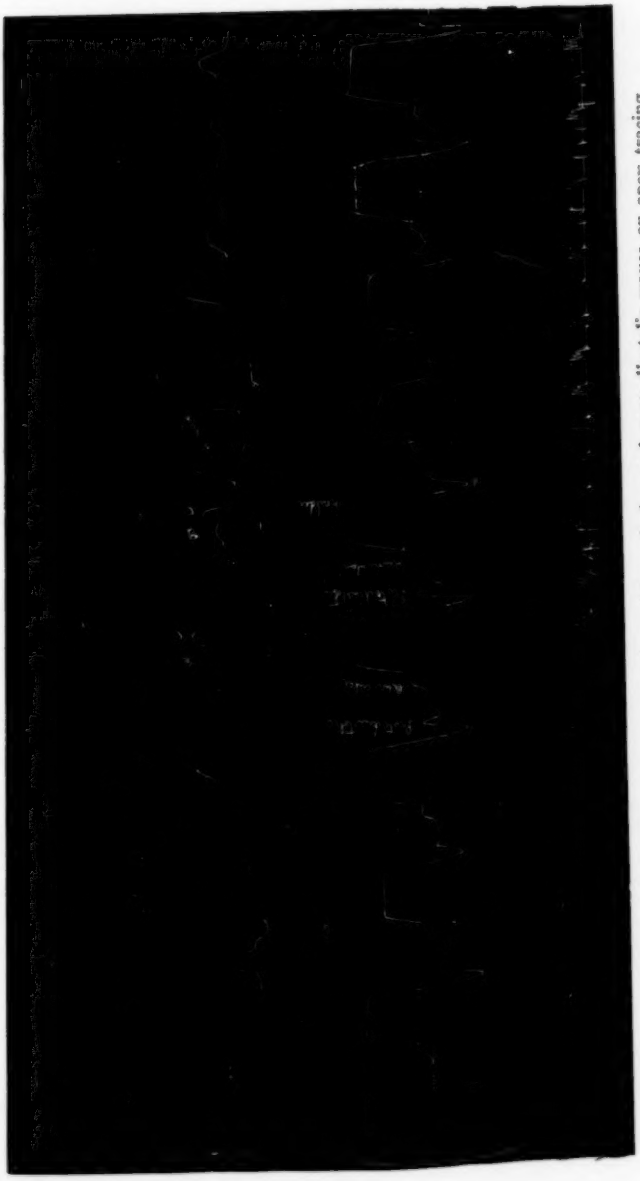

Fig. 6.—Simultaneous apex and venous tracing with auricular and protodiastolic waves on apex tracing.

Effort has been made rather successfully to correlate the conception of the presystolic sound with different pathologic conditions, and to suggest its connection with the presystolic gallop. The sound and shock appear here to be but the accentuation of the normal presystolic sound with its frequently associated presystolic wave on the apex cardiogram. This appears to substantiate the view of Prof. Friedrich Müller that the different gallops represent pathologic exaggerations of events which take place in the normal heart. On searching the literature, it was found that a presystolic sound or "grace note" has been already described by von Wyss, who employs the same technic. His time-results compare very closely with those set forth in the subsequent table.

COMPARISON OF THE ELECTROPHONOGRAMS AND APEX-TRACINGS*

Name	Presystolic Before First	Beginning of Auricular to Beginning of Ventricular Wave
E. W.	0.07 sec.	No auricular
L. G.	No presystolic	No auricular
J. B.	No presystolic	No auricular
C. P.	0.09 sec.	0.12 sec.
J. S.	0.06 sec.	0.08 sec.
E. G.	0.10 sec.	0.10 sec.
C. C.	0.07 sec.	0.06 sec.
B. W.	No presystolic	0.11 sec.
R. T.	0.06 sec.	No auricular
N. B.	No presystolic	0.10 sec.
W. N.	0.08 sec.	0.08 sec.
I. R.	0.06 sec.	0.08 sec.
B. R.	0.08 sec.	0.09 sec.
A. S.	0.07 sec.	No auricular
A. L.	0.06 sec.	0.08 sec.
N. S.	No presystolic	0.08 sec.

* These measurements represent the average of ten sequential beats.

SUMMARY

A presystolic sound, which is generally below the limits of human audibility, is shown on the phonographic tracings of a number of normal boys.

It occurs 0.02 second after the beginning of the auricular wave of the apex cardiogram, 0.07 second before the beginning of the first sound; is of a duration of 0.04 second.

A possible etiologic factor is suggested, the tension of the ventricular walls, and a possible relationship between this sound and the presystolic gallop is called to mind.

It is a pleasure to thank Dr. George Bond of Johns Hopkins Hospital for his interest and assistance in obtaining the tracings.

PERIARTERITIS NODOSA—A CLINICAL AND PATHOLOGICAL REVIEW OF THE DISEASE

WITH A REPORT OF TWO CASES *

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NEW YORK

INTRODUCTION

A number of diseases which are to-day not uncommon and which are recognized clinically without much difficulty were at one time quite rare, owing largely to the fact that so little was known about them that they either escaped notice or were incorrectly diagnosed. It is quite possible that the rather rare but exceedingly interesting affection known as periarteritis nodosa is a case in point. Most of the cases have been observed in Germany, where the disease was first recognized and where the clinicians and pathologists have come to be familiar with it, whereas in this country, where the disease has attracted very little attention, only three cases have been reported up to the present time.[1]

Within the past year at the Presbyterian Hospital, we have had the exceptional opportunity of seeing two cases. Including these, the total number of reported cases now numbers but thirty-eight. Most of the reports have concerned themselves largely with the pathologic histology of the disease and, except for some minor differences of opinion, this aspect of the affection has been well covered. We are still quite in the dark as to the cause, however, and many of the histories are too brief to aid greatly in arriving at a correct idea of the symptom-complex. Indeed, many observers are inclined to the belief that, barring the presence of the subcutaneous nodules, which are present in only a small minority of the cases, there is no set of symptoms on which a diagnosis can be made. One cannot escape the conviction, however, that an increasing familiarity with the disease may lead to some means of diagnosis whereby more cases may be recognized and that the chance for study during life thus afforded may clear up the present obscure etiology. It, therefore, seems most desirable that all cases of periarteritis nodosa be reported as completely as possible. And, in view of the extreme rarity of the disease in this country, the present seems an opportune time for a complete review of the known facts concerning it.

* Submitted for publication, June 1, 1914.

* From the Pathological Department, Presbyterian Hospital, Columbia University, New York.

1. The two cases here given were very briefly reported at the New York Pathological Society during the past year.

REPORT OF TWO CASES

For permission to use the clinical records of these two cases I am greatly indebted to Drs. Janeway, Bovaird and Lambert on whose services in the hospital they occurred.

CASE 1.—Man, aged 26, mechanic, ill about seven weeks, was admitted to the hospital, Dec. 7, 1912. The family history was unimportant.

Past History.—The patient had typhoid at the age of 4. Two years ago he had an attack of grip. Venereal disease is denied. He does not use tobacco; takes an occasional glass of beer.

Present History.—For the past two years patient has had asthma. At first the attacks came about once a month, lately as often as two or three in a week. About three weeks before admission he noticed intense itching about the right ankle and in eight or ten hours an oval, node-like swelling the size of an egg appeared. The overlying skin was tense, shiny and covered with bright red macules measuring about 4 mm. in diameter. The swelling gradually lessened and the macules underwent the color graduations of a contusion. In two or three days the swelling and eruption had entirely disappeared. Pain and tenderness were severe at the height of the swelling, disappearing with its subsidence. The night after the swelling appeared he had a severe asthmatic attack lasting all night. Expectoration was quite profuse and contained clotted blood. Since then he has had a purpuric eruption appearing on different parts of the body roughly every other night with asthmatic attacks on the alternate nights. All parts of his body have been affected except the face. For the past two weeks, accompanying the rash, he has had severe abdominal cramps lasting for ten or twelve hours and ceasing after vomiting. Vomitus consisted of a thin green liquid with a few blood-clots. At times, with the appearance of the eruption he would have pains in various joints and these would be swollen, slightly red, tender and very painful on any motion. Bowels moved once or twice a day and were normal as far as he knows. Appetite is good; no loss of weight; no fever or night-sweats. For the past two weeks patient has been up ten or twelve times at nights to urinate.

Physical Examination.—Pale and sallow. Superficial lymph-nodes slightly enlarged. Eyes normal. Gums firm. No throat lesions. Lungs: Moderate relative dulness at right apex posteriorly; feeble inspiratory murmur with prolonged expiration and high-pitched piping râles over all. Heart: Apex in fifth space, 10.5 cm. to left of mid line; sounds normal, no murmurs. Arteries small, soft and just palpable. Blood-pressure 145-105. Abdomen rather full and tympanitic; liver not felt; edge of spleen just felt at costal margin on deep inspiration; no masses or rigidity. Both legs show numerous small hemorrhagic areas in various stages of involution. These areas vary in size from petechiae to irregular confluent areas about 1 cm. in length. The larger ones are grouped about the ankles and are deep wine color. The lesions are somewhat raised, firm and dry with a tendency to scaling. On the left thigh, just above the knee, there is a large, somewhat elevated, firm area the size of the last joint of the thumb. It is pale green, somewhat tender and apparently in the course of the internal saphenous vein but not connected with it. On the right thigh there is an elongated, raised area measuring 3 by 1 cm. It is reddish brown with dark red spots in the center, is very slightly tender and for its whole length lies over a superficial vein. About the knees there are a few pale green discolorations. Over the lower end of the right tibia there is an irregular depressed ulcer. It is dry and the floor is made up of a deep red blood-clot. Below the left patella there is some thickening in the region of the bursa, with slight pain on flexion of the leg. The most probable diagnosis seemed to be Schönlein's "purpura rheumatica."

Course.—The temperature on admission was 100.4 F., gradually falling to normal on the fifth day. It remained normal for three days and then rose

gradually to 101.8. In a few days it was again normal and then subnormal for five days. There was another short rise to 100.4, followed by another normal period and a terminal rise to 102. The pulse varied between 85 and 130 and was generally more rapid than one would expect for the temperature. When the temperature was subnormal, the pulse was between 80 and 110.

Urine.—Eight examinations. The specific gravity varied between 1.010 and 1.018. There was always a trace of albumin present and on five occasions it was estimated at from 0.15 to 0.22 per cent. No sugar was found. There were always hyaline and granular casts present and at times epithelial and waxy casts as well; also a moderate number of leukocytes and a few to many red blood-cells.

The blood-counts showed the following result:

Date	R. B. C. No.	Hb. Pct.	W. B. C. No.	Polys. Pct.	Lymphos. Pct.	L. Monos. Pct.	Eosin. Pct.
December 9	.....	75	17,200	50	14	2	34
December 10	3,500,000	65	20,200	51	11	0	38
December 12	.....	..	.....	32	12	5	51
December 31	3,384,000	42	20,900	58	17	2	23

December 9: Sputum shows many red blood-cells and ciliated epithelial cells but no Charcot-Leyden crystals, Laennec's pearls or Curschmann's spirals.

December 12: Eye-grounds negative.

December 14: Wassermann reaction (Noguchi modification) negative.

December 17: Since yesterday afternoon patient has complained of constant, sharp abdominal pain without any other change in the physical signs. No vomiting. Stools normal. No tubercle bacilli found in the sputum.

December 18: Phthalein test: Color appeared in twelve minutes. Amount at the end of two hours too small to estimate. Sputum bloody. Coughs less. Feels better. Abdominal pain has disappeared. Lips and nails quite cyanotic. No tubercle bacilli in sputum.

December 20: Slight pain in the shoulders and neck this morning. Has a considerable amount of yellowish-green sputum with considerable fresh blood. The lungs show nothing more than the signs of asthma and bronchitis. No pain in the chest. Considerable relief from epinephrin.

December 29: White, rather glistening lines are seen along the vessels of the left retina as they come through the disk.

December 31: Gastric contents: Total acidity, 38. Free hydrochloric acid, 6. No lactic acid. Moderate reaction for blood. No ova or parasites in the stool. A second phthalein test showed the color in seventeen minutes, but the amount at the end of two hours was again too small to estimate.

January 1: The veins and glands in both inguinal regions are very sore and tender. In the left femoral region there is a small, red, tender area.

January 2: There is more redness and swelling in the left femoral region. On the back of the left leg there is a slightly swollen, reddened area measuring about 4 by 6 cm. The right hypochondrium is distinctly tender and resistant.

Jnuary 5: There is a pericardial friction-rub present this morning and a pleural friction-rub at the left base. Lumbar puncture: Twenty c.c. of clear fluid obtained. Cultures sterile. Urea, 0.323 per cent. Sodium chlorid, 0.812.

January 6: Died to-day after increasing stupor for two days. Gradual failure of pulse and respiration before death. During the last sixty hours voided only 1,000 c.c. of urine. The blood-culture taken in two-broth flasks, January 3, remained sterile. Blood-pressure varied between 135 and 165. The urine quantity varied between 690 and 1,920 c.c. On thirteen days it was below 1,000 c.c.

Post-Mortem Examination.—The diagnosis of periarteritis nodosa was not suspected at the time of the necropsy. When the microscopic sections were examined several days later and the characteristic lesion found in the kidney, the organs from the patient were again carefully examined; but the only sug-

gestion of arterial lesions was found in the heart, where there were one or two pin-head-sized whitish nodules on one of the small coronary branches. No nodules were found in any of the other organs. Unfortunately, none of the subcutaneous tissue in the regions of the eruption and swellings was examined.

The essential points in the necropsy were the following:

The body is strikingly pale and considerably emaciated. There are ecchymoses about the right knee and about both elbow-joints. The peritoneal cavity contains a small amount of cloudy yellow fluid, and the intestines show a scattered fibrinopurulent exudate. The lungs are adherent to the chest-wall and to the outer surface of the pericardium by fresh fibrinous adhesions.

Lungs: Both are edematous and show scattered areas of bronchopneumonia. The bronchi are intensely congested and contain mucopurulent material. The vessels appear normal.

Bronchial Lymph-Nodes: Moderately enlarged, deeply pigmented and firm.

Heart: The pericardium contains about 50 c.c. of cloudy yellow fluid; there are several fresh fibrinous adhesions stretching between the two surfaces and the surfaces are covered with a shaggy, fibrinopurulent exudate and show scattered petechial hemorrhages. The heart is not enlarged. There is a small, firm, irregular nodule at the base of one of the pulmonic cusps and the mitral cusps show small, irregularly nodular, reddish vegetations, the largest about the size of a small pea. The other valves and the heart chambers show no change. In general the heart-muscle is homogeneous and dull reddish-brown, but there are scattered areas of a more dirty yellow color. The main portions of the coronary arteries show no sclerosis. The aorta is smooth and elastic throughout its course.

Spleen: Measures 12 by 7 by 3 cm. There is perisplenitis. Otherwise the organ appears normal.

Liver: Measures 29 by 19 by 6 cm. There is a small area of superficial atrophy in the right lobe. On section, the liver shows no abnormal change.

Gall-Bladder: Normal. Ducts patent.

Kidneys: Left measures 12 by 7 by 3.5 cm. The capsule strips easily, exposing a smooth yellowish-pink surface with a rather diffuse mottling of yellow. On section the cortex does not average more than 5 mm. in thickness and is slightly less than this in some places. The striations are indistinct and quite distorted. The glomeruli are quite distinct as colorless dots. The pelvis and ureter are normal.

Right: Measures 11.5 by 6 by 3.5 cm. and is quite similar in all respects to the left.

Adrenals and esophagus appear normal.

Stomach: Contains a little brownish fluid and a moderate amount of mucus. There is considerable injection of the mucous membrane and a few small petechial hemorrhages.

Pancreas and Ducts: Normal.

Mesenteric Lymph-Nodes: These are enlarged, many to bean-size. Several of them are broken down and ooze creamy-yellow pus on section.

Intestines: Show nothing more than a few areas of congestion in the lower part of the ileum.

Bladder and Prostate: Normal.

Brain and Spinal Cord: Permission could not be obtained for their examination.

Microscopic Examination.—Lungs: Many sections from various parts of the lungs were examined. These show a thickened pleura, extensive pulmonary edema with congestion of the alveolar walls and swelling of the alveolar epithelium and scattered areas of hemorrhagic bronchopneumonia. There is some increase of connective tissue about the bronchi together with numerous mononuclear wandering cells and eosinophils. Scattered here and there in the alveoli are small clumps of Gram-positive cocci. The large vessels appear quite

normal and in most of the sections even the smaller arteries show no change; but one does find a few small arteries both about the bronchi and in the lung-tissue proper which are not normal. The changes consist in an adventitial and periarterial infiltration with mononuclear wandering cells and eosinophils, polymorphonuclear leukocytes being almost entirely absent. The changes are generally unilateral or at least more marked on one side, and the media and intima are normal. An occasional small artery is seen, however, whose lumen is almost entirely occluded. These changes apparently represent an early stage of the lesion seen in the arteries in other organs.

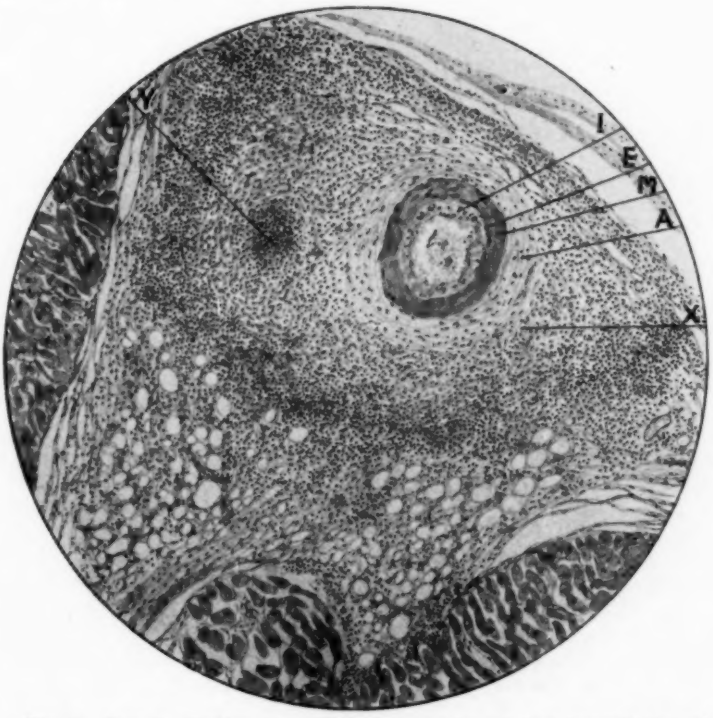

Fig. 1.—Case 1. Section of a small coronary branch just beneath the epicardium showing very pronounced periarterial infiltration with a small area of beginning necrosis on one side. The media, while still intact, takes the eosin stain rather strongly. *I*, intima; *E*, internal elastica; *M*, media; *A*, adventitia; *X*, periarterial infiltration; *Y*, area of beginning necrosis.

Bronchial Lymph-Node: In the capsule, two small arteries are found showing early changes similar to those seen in the lung. The arteries in the gland itself show no change. There is considrable pigmentation and hyperplasia.

Vegetation of Mitral Valve: Consists of a very vascular and quite cellular mass of connective tissue richly invaded by mononuclear wandering cells. On the surface is an irregular thrombus mass containing clumps of bacteria. These appear to be cocci. Smears from these vegetations show a few pairs of cocci surrounded by a small space and also some rather fat Gram-positive bacilli.

Heart: The pericardium shows an acute inflammatory exudate. There is cloudy swelling of the muscle-fibers and patchy interstitial myocarditis about the vessels. A section of one of the papillary muscles shows a most extensive fibrosis with large areas of granulation tissue and wandering-cell infiltration. Most of the vessels show no change. Some of the small arteries, while showing no changes in their coats, have a little surrounding cellular infiltration, the cells being generally mononuclear wandering cells and eosinophils. One section, taken through one of the tiny macroscopic nodules, shows the periarterial character of the lesion very well (Figure 1). It affects a small artery just beneath the pericardium. The lumen is narrowed, being encroached on by the moderately proliferated intima, and contains red blood-cells, among which are some fibroblasts extending in from the intima. The intima is thicker on one side, its texture quite loose and its cells irregular in size and shape. Some of

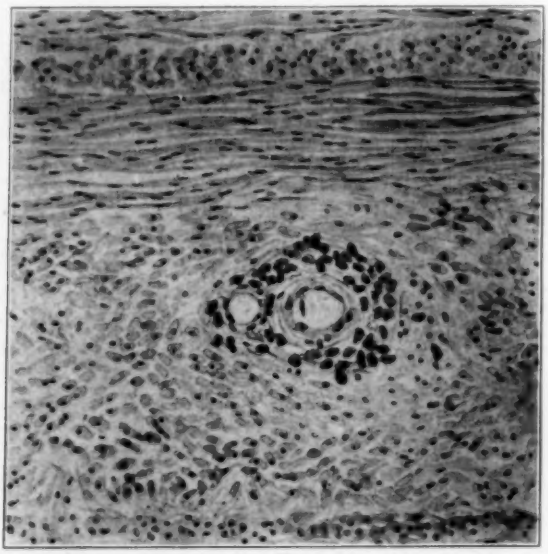

Fig. 2.—Case 1. Section of a small artery in the muscular coat of the stomach. Represents a very early lesion. The intima and media are normal. The elastic lamellae are not changed. The adventitia is loose in texture and is densely infiltrated with eosinophils.

them are quite definitely fibroblasts; others look like distorted endothelial cells. The internal elastica is well preserved except at one point, where it is wanting opposite a small necrotic area in the media. The media appears granular and the nuclei indistinct but it shows no cellular infiltration. There is no characteristic hyaline ring, but the media gives one the impressioon of approaching toward such a condition as seen in other vessels. The fibers appear more granular and take the eosin stain more intensely. The adventitia is much thickened and merges imperceptibly into the tremendous periarterial cellular infiltration and granulation tissue. The cells are wandering cells, fibroblasts and a most striking number of eosinophils. Many of them are plasma-cells. While polymorphonuclear leukocytes are scarce, one does find some. All of these cells infiltrate the surrounding fat for a considerable distance. At one side there is a small area of necrosis.

Spleen: Eosinophils are rather strikingly numerous and seem especially attracted to the vessels. The small arteries are somewhat thickened but none of them shows any characteristic change.

Liver: Shows cloudy swelling and one small area of superficial atrophy. Some of the portal spaces show a little increase of connective tissue with a few wandering cells. There are no distinct arterial changes.

Pancreas: Shows no change except for a little wandering-cell infiltration about one or two of the small arteries. Mixed with these cells are a few eosinophils.

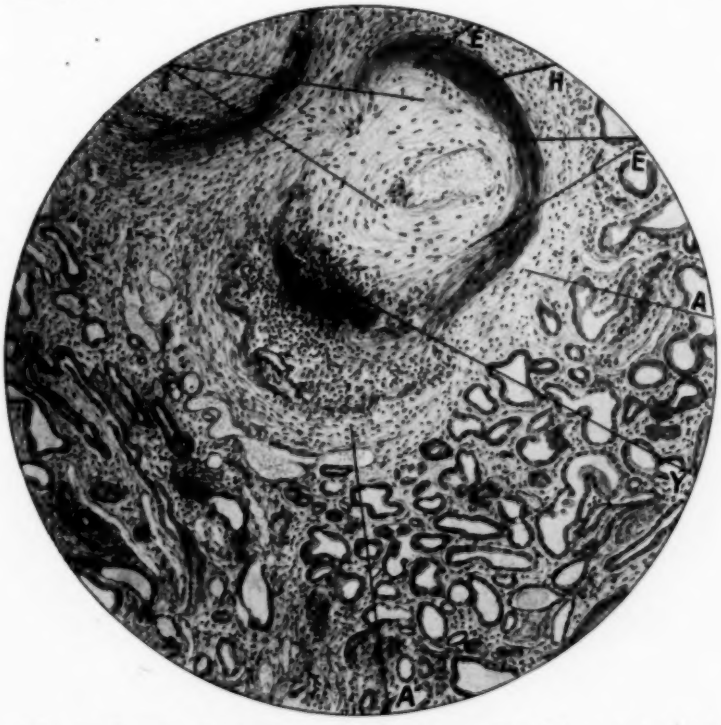

Fig. 3.—Case 1. Section of artery in kidney. The intima, *I*, is much thickened and is surrounded for two-thirds of the circumference by the internal elastic lamella which does not show in drawing. Just external to this is the hyaline ring, *H*, which fuses with the area of necrosis at *Y*. Adventitia, *A*, apparently extends outside the area of necrosis. *E*, internal elastica as shown in other sections stained with elastic-tissue stain. It is wanting opposite the area of necrosis.

Mesenteric Glands: Many small arteries are seen both within the gland and in the surrounding tissue which show early changes.

Stomach: The various coats of the organ appear normal. In one section, in the muscular coat, there is a cross-section of a small artery (Figure 2) which is of interest as it possibly shows a very early lesion. The intima and media appear normal and the elastic lamellae are unchanged. The adventitia is loose

in texture and cannot be differentiated from the adjacent tissue. It is densely infiltrated with eosinophils and a few cells with large, oval, vesicular nuclei. No further change is made out in tracing the vessel through serial sections. While one cannot be certain that this represents a very early change, the eosinophils which are found so abundantly in the lesions elsewhere seem to point to this conclusion. Another section shows a typical lesion of a small artery in

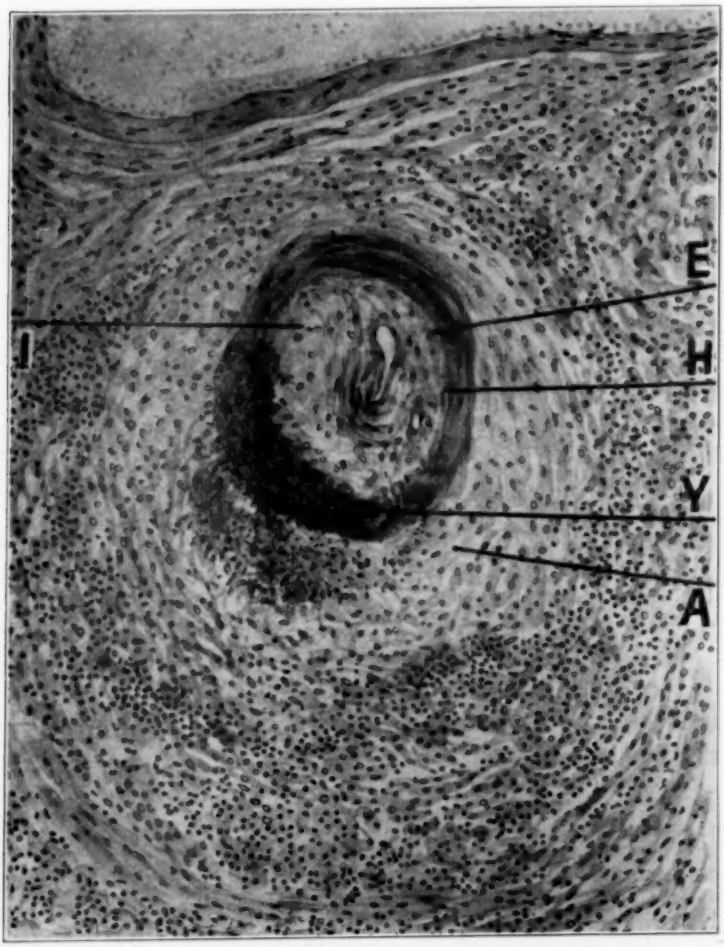

Fig. 4.—Case 1. Section of artery in adrenal. The intima, *I*, is thickened. The internal elastica, *E*, is intact except in the region of necrosis, *Y*, where it has disappeared. The hyaline ring, *H*, in which one can still make out the cells of the media lies just external to the elastica and fuses with the area of necrosis at *Y*. Adventitia, A, merges imperceptibly with the periarterial infiltration.

the submucosa. An elastic-tissue stain shows the internal elastica ending abruptly after encircling about one-half the circumference while the external elastica is completely gone. Another vessel shows similar changes but with an added complete thrombosis.

Intestines: There is an acute inflammatory peritoneal exudate, intense congestion of the vessels and some hemorrhages in the mucosa. A number of the small arteries show typical early changes and two are completely thrombosed.

Kidneys: These show the most striking changes of any of the organs, and it was here that the lesion was first noticed. In this place (Figure 3) the lumen of the artery is small and the intima very much thickened, being composed of a loose connective tissue, rich in fibroblasts and containing a few eosinophils and nuclear fragments. Surrounding the intima for about two-thirds of the circumference, the internal elastica is intact but swollen in places. Just outside of it and limited by it, is the characteristic, intensely eosin-stained, hyaline ring in which one can still make out the cells of the media. It gives the impression of being a more advanced stage of the appearance seen in the section of a coronary artery. At one side, the elastica has disappeared, the hyaline ring melts into an area of necrosis and the cellular infiltration of the adventitia breaks through into the intima. The adventitia is composed of young connective tissue with some wandering-cell infiltration and at this point seems to extend outside the area of necrosis which is mainly in the media. While this is the most advanced lesion seen in any of the many kidney-sections, many of the small arteries show similar if less marked changes. There is an exquisite acute, subacute and chronic glomerulonephritis, the glomeruli showing all stages of adherence to the capsules with epithelial crescents and hyaline thrombi. There is an extensive diffuse increase of connective tissue throughout and a striking wandering-cell infiltration with many eosinophils in the interstitial tissue. The vessels are all congested and many of the tubules contain blood. Some of the tubules are practically obliterated while some are dilated and cyst-like.

Adrenals: The arteries of the capsule show the lesion beautifully, the hyaline ring being especially well marked (Figure 4). As in the kidney, this ring is situated just outside the internal elastica which is preserved for about two-thirds of the circumference and then melts into an area of intensely eosin-stained necrosis in the media. The intima is loose in texture and rather loculated. The cells are large and contain oval, vesicular nuclei. There is an intense periarterial exudate and granulation tissue with many eosinophils. The gland itself shows no change.

Bacteriologic Findings at Necropsy.—Heart-blood: Two broth-flasks show colon bacilli and Gram-positive cocci in chains. The latter were overgrown by the former and were not isolated.

Peritoneal Exudate: Smears show pus-cells and many chain cocci. No other bacteria. Cultures give a pure growth of streptococci.

Pericardial Fluid: Smears show unformed detritus, rarely a pus-cell. No bacteria found. Cultures in broth and ascitic glucose-agar are sterile.

Mesenteric Lymph-Node: Smears show cocci in chains and many pus-cells. Cultures not taken. Unfortunately the cultural characteristics of the streptococcus isolated from this case were not worked out so that it is impossible to compare it with the organism obtained in the second case.

Careful examination of many sections stained for bacteria by various methods failed to show any in the vascular lesions in spite of the fact that the necropsy cultures showed a bacteremia. No spirochetes could be found in sections stained by the Levaditi method.

Case 2.—Girl, aged 10, ill five weeks, was admitted to the hospital Jan. 18, 1914. The family history was negative.

Past History.—Five years ago patient had a slight attack of pain in the epigastrium somewhat similar to the present attack but less severe. It lasted only one day. Had measles as a baby and diphtheria five years ago.

Present History.—Nine days before admission patient was taken suddenly ill in the night with severe pain in the epigastrium. Felt better the next day and was up and about for two days, when the pain came on again and she vomited twice. The pain was sharp and well localized to a small area high up in the midline. Since that time she has been in bed and has had the pain intermittently but always in the same place; has felt feverish, had a headache and has vomited several times. Her throat was sore but has been better for the last few days. She says that she had blood in her sputum at times. No pain is felt on micturition and no blood appears in the urine.

Physical Examination.—Patient well developed and large for her age. Appears acutely ill. No eruption present.

Pharynx: Reddened and shows a considerable thin mucoid, blood-tinged exudate. The left tonsil is enlarged, the right slightly so.

Tongue: Dry and heavily coated.

Lymph-Nodes: The anterior cervical and axillary are palpable.

Heart: Is not enlarged, sounds regular and of good force. No murmurs. Pulses equal and regular. Low tension. Walls not palpable.

Lungs: Clear except for a few transient râles at the left base.

Liver and Spleen: Not palpable.

Extremities: Reflexes normal. No edema.

Abdomen: There is general abdominal fulness and resistance which seems involuntary. No true rigidity. There is tenderness over the whole lower abdomen, more marked on the right side. No dulness in the flanks. No masses. The temperature on admission was 102.6 F. and the blood-count showed 33,100 leukocytes with 93 per cent. of polymorphonuclear leukocytes. A diagnosis of appendicitis was made and she was operated on shortly after entering the hospital. The appendix and peritoneal cavity were found to be normal. The abdomen was explored but no cause found for the symptoms.

January 20: Blood-culture, two broth-flasks sterile.

January 21: There is tenderness and evidence of fluid in both knee-joints and tenderness in both hip-joints. Heart normal.

January 22: There is tenderness in the left shoulder-joint. Temperature between 102 and 103. Wassermann reaction, three plus.

January 23: Shoulder still painful. Signs in the knees have cleared up. Heart normal. Chill.

January 27: Right knee shows a small amount of fluid. Slight amount of edema in the region of the Achilles tendon of both legs. The abdomen is distended in its upper half but not tender. No dulness in the flanks. Spleen not palpable. Heart and lungs normal. There is a little edema of the dependent part of the back.

January 28: Throat culture shows a predominant streptococcus. Patient seen by Dr. Janeway, who believes that she is suffering either from sepsis following a streptococcus sore throat and has a toxic nephritis or that she has nephritis following an unrecognized scarlet fever. Transferred to the medical service. During her stay on the surgical side the urine showed a specific gravity of between 1.012 and 1.028. Albumin, from a very faint trace to a trace. A few to many hyaline and granular casts. No red blood-cells. A blood-count taken January 19 showed 26,200 leukocytes with 92 per cent. of polymorphonuclears, and one taken January 28 showed practically the same. The temperature varied between 101 and 103.6 for a week. It was then lower reaching normal January 27 and on the following two days was between 99 and 100.4. The pulse corresponded with the temperature, varying between 74 and 128. The surgical diagnosis was acute tonsillitis, acute nephritis and acute toxic arthritis. She was apathetic at times, quite thirsty and vomited repeatedly.

On admission to the medical ward her physical examination was unchanged. There was tenderness over the whole abdomen, most marked in the midline

above the umbilicus. Very slight edema of the back. The right wrist was somewhat stiff and painful on motion. The right shoulder was somewhat painful.

January 29: White blood-cells, 17,000; polymorphonuclears, 95 per cent.; lymphocytes 5 per cent.

February 1: Liver felt 2 inches below the costal margin. White blood-cells, 52,000; polymorphonuclears, 95 per cent.; lymphocytes, 4 per cent.; large mononuclears, 1 per cent.

February 2: Blood-culture, two broth-flasks sterile. Patient is quite drowsy. There is a mottled erythema over the upper part of her forearms.

February 3: White blood-corpuscles, 66,000; polymorphonuclears, 95 per cent.; lymphocytes, 5 per cent. There is a systolic murmur at the apex. The eruption has disappeared. General condition improved. The right wrist is swollen and painful on motion.

February 5: White blood-corpuscles, 39,800; polymorphonuclears, 90 per cent.; lymphocytes, 9 per cent.; large mononuclears, 1 per cent. Wassermann reaction negative. Blood-culture, two ascitic glucose-agar plates, sterile.

February 6: Metacarpophalangeal joints of both hands swollen and tender. Right wrist better. There is a dusky mottling of the face, whole trunk and extremities, especially over the back and shoulders. It is in the nature of a diffuse erythema.

February 7: Vomitus, 175 c.c. of thick yellow fluid. Total acidity 24, no free hydrochloric acid. Faint reaction for lactic acid. Blood-count: White blood-corpuscles, 40,400; polymorphonuclears, 73 per cent.; lymphocytes, 27 per cent.

February 10: Temperature is lower and joints have cleared up. For the past three days has suffered from paroxysms of abdominal pain and complains of pain on the slightest pressure. There is no rigidity. Rectal examination negative.

February 11: White blood-corpuscles, 26,600; polymorphonuclears, 88 per cent.; lymphocytes, 12 per cent. Vomitus, 155 c.c. of a dark brownish fluid. Faint reaction for blood. Total acidity 8, free hydrochloric acid 4. No lactic acid. Stool: Yellow, fluid; contains small flecks of mucus; moderate reaction for blood; urobilin, moderate. Microscopic examination: Mucus, red cells, pus-cells and epithelial cells. No ova or parasites.

February 14: Patient died. For the preceding week was very apathetic and disliked to be moved or examined. Lay on her side with legs drawn up. At times severe abdominal pains were present which generally required morphin for relief. The pain seemed to be more in the region of the umbilicus. There was tenderness or hyperesthesia over the whole abdomen, but no resistance or rigidity. No signs of fluid. Vomited two or three times a day, generally after taking food. On the day of death, suddenly awoke early in the afternoon, cried out on account of severe abdominal pain, attempted to throw off the bedclothes, became very cyanotic and had a very rapid, almost imperceptible pulse. Relieved by morphin and went to sleep. About three hours later she cried out again, gave a few gasping respirations and died.

Her temperature varied between 99 and 103.2, during the last week between 99 and 101.5. Pulse corresponded, in rate, ranging between 74 and 120. Blood-pressure, from 104 to 60. Urine: Twelve examinations showed the specific gravity quite constant between 1.012 and 1.018, with from a trace to a very faint trace of albumin, generally a very faint trace. Most of the examinations showed hyaline and granular casts. The amount of urine varied between 150 and 1,600 c.c., being 1,000 c.c. or over on only three occasions.

Post-Mortem Examination.—Two and one-half hours post mortem. The body is that of a strikingly pale, moderately wasted young girl. There is a little puffiness of the eyelids and slight edema of the ankles. No subcutaneous nodules found. The abdomen is moderately distended. None of the joints

appears swollen. The abdomen contains about 300 c.c. of clear amber fluid. The peritoneal surfaces are smooth and glistening except for a few small shreds of fibrin over the intestinal coils. The appendix is missing, the omentum being adherent to the stump. No nodules seen on any of the vessels. On opening the thorax, the lungs are found partially collapsed and retracted, exposing a large precordial surface. There is about 100 c.c. of clear fluid in each pleural cavity and the same amount in the pericardial sac. The diagnosis was immediately apparent on exposing the heart, the coronary branches showing numerous characteristic nodules (Fig. 5). The heart weighs 320 gm.

Fig. 5.—Case 2. Heart showing thickly set nodules on coronary branches with overlying petechial hemorrhages.

Right Coronary: At the origin of the infundibular branch there is a globular swelling measuring 6 mm. in diameter, filled with a grayish-red adherent thrombus. Near the termination of this branch there is a small yellowish-white nodule of about 2 mm. in diameter. The transverse branch is almost occluded by connective tissue but shows no nodules. The marginal branch shows a small aneurysmal dilatation, partially filled with thrombus just after it leaves the main artery. In the rest of its course and in its branches are numerous, often closely set, oval and globular, firm swellings, the largest measuring about 3 mm. in diameter. On section, these appear as partially occluded vessels with a very thick whitish periphery. The descending branch shows no external change.

Left Coronary: The main stem is free. The first portion of the descending branch is quite tortuous and contains a thrombus. A little further on there is a bluish-red aneurysm measuring 1 by 0.5 cm. and showing a few petechial spots over it. It is filled with a thrombus. Near the apex there are a few firm nodular swellings. The transverse branch shows similar nodules and in the branches

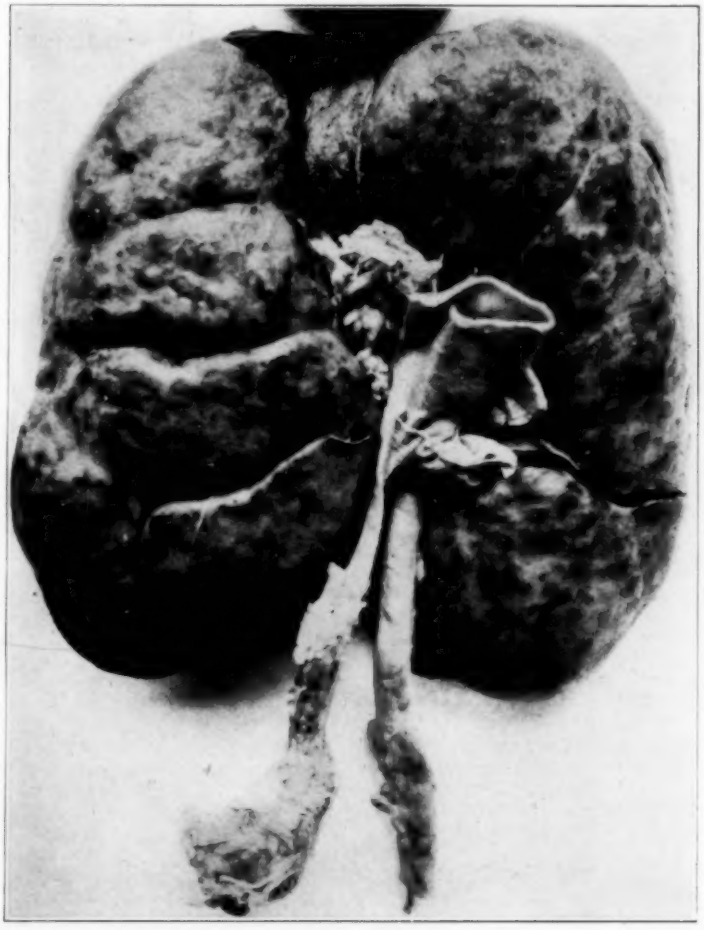

Fig. 6.—Case 2. External view of kidney showing numerous dark raised areas due to hemorrhagic infarcts separated by sunken grayish tissue. The main renal artery and branches show no nodules.

which it gives off over the anterior and posterior surfaces of the ventricles there are numerous firm nodules, the largest measuring 2 or 3 mm. in diameter. Over these, discrete and conglomerate petechial hemorrhages are numerous. A section through any portion of the heart-wall shows the arteries very much

thickened, the lumen generally completely occluded or represented by a minute reddish dot and the adjacent muscle showing irregular yellowish opaque areas. The veins are not changed. The valves and the various chambers of the heart are all quite normal. The aorta and large branches show no change.

Lungs: Except for a moderate collapse, the lungs appear quite normal and one cannot make out any changes in the vessels or bronchi.

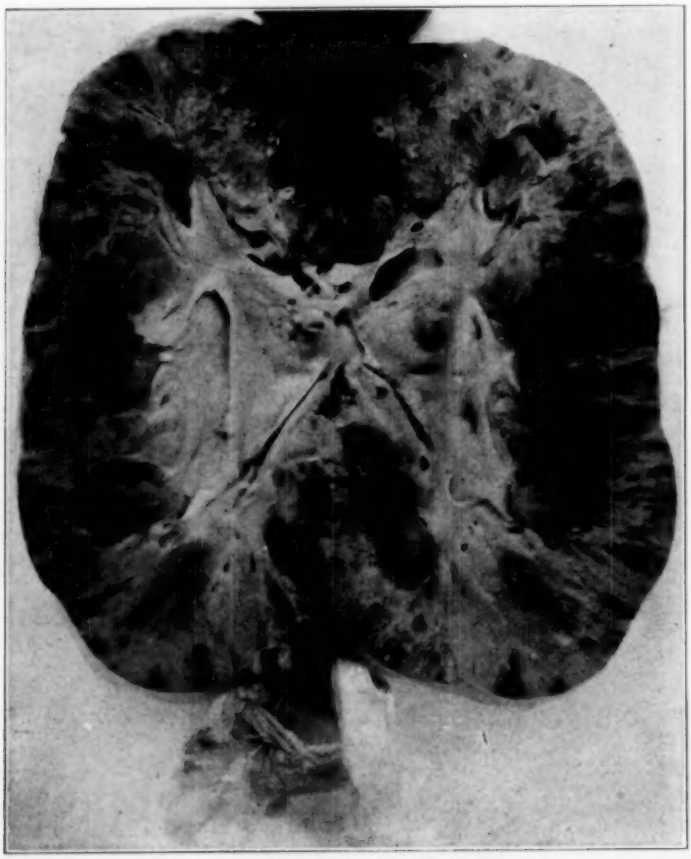

Fig. 7.—Case 2. Same kidney as Fig. 6, seen on section. Shows the infarcts distinctly. The numerous little nodules along the small arteries can also be made out.

Liver: Weighs 1,400 gm. The surface is smooth and brownish yellow with irregular areas of congestion. On section, the tissue about the portal vessels appears a little increased in amount and the vessels a little thickened. No definite nodules seen.

Gall-Bladder: Contains viscid greenish bile. The mucosa appears normal and the ducts are patent.

Spleen: Weighs 160 gm. The capsule is tense but smooth and the organ is quite firm. The cut surface remains quite flat and the pulp is firm. The color is purplish red and the malpighian corpuscles are unusually numerous and larger than normal. One obtains the impression that the small central arteries are slightly thickened.

Pancreas: Is large and of normal consistency. On section, it shows nothing abnormal. No macroscopic lesions of the arteries can be seen.

Stomach: Appears quite normal. No lesion of any of the vessels.

The esophagus, trachea, larynx, thyroid and parathyroids appear normal.

Kidneys: Are quite alike (Figs. 6 and 7). The left weighs 160 gm. and the right 150 gm. The fatty capsule is moderately thick but strips easily. The true capsule is easily removed without tearing the renal surface which has a most remarkable appearance. It is coarsely irregular and in color, a mottled red and opaque yellowish gray with a sprinkling of small yellowish points. The raised portions are a deep red with small gray dots. They are abundant, in the aggregate representing fully one-half of the surface, are quite irregular in outline, several often running together to form map-like patterns and they are separated by slightly sunken, dull, opaque, yellowish-gray tissue containing flecks of yellow. The same appearance is seen on section. The cortex averages from 6 to 8 mm. in thickness. The vessels of the pyramids are much congested. The cortex and tissue between the pyramids has a rather rough, furred appearance and one can make out numerous, small, hard pearly gray nodules along the course of the vessels. These resemble miliary tubercles. There are many, larger and smaller, deep red and more grayish-red, necrotic-looking, roughly wedge-shaped areas extending from the surface deeply into the cortex and in places into the medulla. These correspond with the raised areas on the surfaces. They are separated by slightly sunken, yellowish-gray opaque tissue in which are tiny nodules and flecks of yellow. The main renal arteries and their larger branches show no change. An attempt was made to inject the kidney but no gelatin could be forced through the vessels. The kidneys were almost exactly like the colored illustration in Dickson's article.

Adrenals: These are of normal size. On section there are several small vessels which seem thickened and show thrombi.

Uterus: Undeveloped. The tubes, vagina and ovaries all appear normal.

Intestines: Duodenum normal. In the ileum, there are two small, widely separated areas which show a little hemorrhage of the crests of the rugae. In the cecum, there is a small cavity at the appendix stump filled with reddish, grumous material. Otherwise the intestines show no change and the vessels are quite normal in appearance.

Omentum and mesentery are normal.

Mesenteric lymph-nodes: Moderately enlarged and show some thickened vessels with thrombi but no definite nodules.

Arteries: The celiac axis and its branches show no change. In fact, none of the larger arteries shows anything abnormal. The veins are quite normal. The blood in all the vessels is quite fluid. Permission could not be obtained to examine the nervous system, joints or extremities.

Microscopic Examination.—Heart: In one section, taken at a distance from the region of the nodules, the muscle appears fairly normal. The striations are distinct and the vessels quite normal but congested. Around one small vessel there is a little infiltration with wandering cells penetrating between the muscle fibers. Among these cells there are a few eosinophils. In another section there are several irregular areas of fibroblasts replacing the muscle-fibers. A section through the largest aneurysmal nodule shows a fair sized, dilated vessel completely filled with an adherent thrombus which shows an invasion of fibroblasts from the vessel-wall. The wall is much changed. Only in one small area is the internal elastica present and here it is in direct relation with the thrombus. Immediately external to it there is a ring of intensely eosin-stained material in

which nuclei are still seen. In places, the media appears rarefied and shows spaces, in other regions the vessel-wall is composed of fibrous granulation tissue. The adjacent heart-muscle shows granular degeneration and irregular fibrous-tissue replacement. Near the aneurysm there is a smaller vessel seen in cross-section. One can make out a delicate endothelial lining, external to which there is a very loose tissue, internal elastica, homogeneous hyaline ring and a marked adventitial infiltration with mononuclear wandering cells and fibroblasts, among them an occasional eosinophil. The adjacent heart-muscle is granular and degenerated and shows considerable fibrous tissue. Another vessel is seen in which the infiltration is largely perivascular. A final heart-section shows a large artery filled with thrombus showing beginning organization about the periphery. The heart-muscle is cloudy and shows scattered wandering cells and considerable fibrous tissue. In the artery, the elastica is quite gone. The homogeneous hyaline ring is quite distinct close to the intima and at one point it splits into two layers enclosing a granulation tissue containing beautiful fibroblasts and hemorrhage. The perivascular tissue is very cellular, showing fibroblasts, wandering cells and many eosinophils. A longitudinal section of a small vessel shows the coats normal but a considerable similar cellular exudate in the perivascular tissue. Eosinophils are numerous. A cross-section of another vessel shows the lumen filled with beautiful granulation tissue and in another there is canalization of the thrombus.

Aorta: Appears normal. Several small branches at the side of the aorta show characteristic changes of a rather late type.

Lungs: The lung-tissue shows slight collapse with some thickening of the alveolar walls. Sections taken near the surface show no vascular lesion either in the pulmonary or bronchial arteries. Sections from the hilum show very pretty lesions of the bronchial arteries but none of the pulmonics. There is a small lymph-gland present in which eosinophils are very numerous.

Bronchial Glands: The follicles are moderately well shown. The sinuses are dilated and contain relatively few cells. One or two small arteries are seen which show the changes seen elsewhere, eosinophils being quite numerous. Some of the follicles show hyaline degeneration.

Spleen: This is much congested, the blood-spaces showing up very clearly. In some of the malpighian corpuscles there is hyaline degeneration of the central cells. In one section, there is an irregular area of infarction. Eosinophils are quite numerous throughout. Several of the small arteries show characteristic changes. In some, the lesion appears as an adventitial cellular infiltration, with a rather marked invasion of the media with wandering cells and fibroblasts, the muscle being almost entirely replaced. In one or two of the small arteries of the malpighian corpuscles there is a fringe of cells just outside the adventitia, most of which are eosinophils.

Liver: The cells show cloudy swelling and in many places vacuoles. In most of the portal spaces there is an infiltration of wandering cells and eosinophils, often quite definitely about the arteries. In a few of the arteries the lesion is quite definite. Another section so taken as to give a longitudinal view of the vessels and bile-ducts gives a very good picture of the lesion and shows considerable surrounding fibrosis.

Pancreas: The lesions here are exquisite. In general, the parenchymal cells and islands are normal, but there is a moderate increase in the fibrous tissue between the lobules. In one region, there is a definite area of necrosis, apparently an infarct, the supplying arteries being severely changed. The striking thing in the section is the lesion of the vessels. Almost every artery shows most extensive changes and there is a very marked perivascular wandering-cell infiltration with fibrosis. One of the prettiest lesions in the whole case is seen in a longitudinal section of a small artery (Fig. 8). At one end the artery is perfectly normal. It then shows a wider and more irregular lumen with a moderately thickened intima in which are various-sized irregular nuclei, an internal elastica which is more or less preserved until one reaches the region

of most extensive change where it gradually fades out, a homogeneous hyaline band on either side of the vessel which is in places internal to the elastica, in other places external and for some distance divided by it. External to this one cannot differentiate between media and adventitia. One comes on a loose mass of various-sized wandering cells and eosinophils with a few fibroblasts and outside of these a young connective tissue with numerous eosinophils. In serial sections, the lesion can be traced into normal artery once more.

Esophagus: The lesion is seen in one or two of the small arteries of the serosa.

Stomach: Normal. One small artery is seen in the muscularis with a little cellular infiltration about it.

Colon: A longitudinal section of a small vessel shows it normal but on either side of its wall the branches show extensive changes.

Ileum: Normal.

Cecum: One vessel shows the lesion. External to the cecum there is an area of granulation tissue the borders of which are necrotic. This represents the softened area at the base of the appendix described in the gross. Appendix is normal.

Mesenteric Lymph-Nodes: Appear much the same as the bronchial.

Lymph-Node at Gall-Bladder: Shows various areas of hyaline degeneration but no vascular lesions.

Thyroid: Normal. Vessels unaffected.

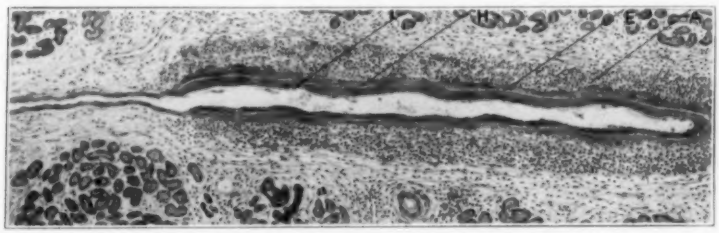

Fig. 8.—Case 2. Longitudinal section of artery in pancreas. The rather abrupt beginning of the lesion is well seen at the left. The intima, *I*, is thickened and is indistinguishable from the hyaline ring, *H*. The internal elastica, *E*, thus apparently divides this hyaline ring. The media is represented by the hyaline ring and the adventitia, *A*, merges with the periarterial infiltration. In other sections the lesion can be traced to the right into normal artery again.

Kidneys: Sections show very numerous fresh hemorrhagic and older infarcts. A large portion of the cortex is thus affected and the infarcted areas often run down to and into the medulla. The small amount of intervening renal tissue is fairly normal except for the vascular changes which are very extensive, almost every small artery being affected. There is considerable perivascular infiltration. One fairly large artery shows an extensive thickening of the intima, the internal elastica remaining intact. The thickening consists of a bluish-pink material rich in spindle-shaped fibroblasts, many of the cells having peculiar little spaces about them. The media is composed of a similar tissue while the adventitia is more fibrous. The other vascular lesions are merely repetitions of the changes seen elsewhere.

Adrenals: Several of the small arteries about the organ show characteristic lesions. There are several infarcted areas in the cortex.

Fallopian Tube: One vessel found which shows typical changes.

Ovary: Normal.

Psoas Muscle: One small artery is seen which shows a beginning infiltration about the adventitia. The muscle-fibers are normal.

Pectoral Muscle: Very distinct changes are seen about many of the small arteries, the muscle-fibers remaining unaffected.

Uterus and Bladder: Normal.

Bacteriologic Findings at Necropsy.—Heart-Blood: Cultures were taken in various mediums, two ascitic glucose-agar shake-cultures, three ascitic glucose-agar slants and one neutral broth. These all remained perfectly sterile. At the end of three weeks they were examined, although there had been no sign of any growth. At present, three months after the necropsy, no growth has appeared.

Peritoneum: Cultures showed a *Staphylococcus aureus.*

Pericardial Fluid: One tube remained sterile, the other showed a colon bacillus. The most promising field for obtaining successful cultural results seemed to lie in the examination of the cardiac nodules and consequently most of the attention was directed to them. In the first place numerous smears were made from these nodules. These were stained by various methods but gave entirely negative results. The largest aneurysmal nodule was excised and washed in three changes of sterile salt solution. It was then divided into two portions, using Rosenow's sterile method. One portion was ground up in sterile salt solution. Of this, one guinea-pig received 0.5 c.c. intraperitoneally, one received 1 c.c. intraperitoneally and two rabbits received 0.5 and 1 c.c. respectively, intravenously. All of these animals remained perfectly well. They were finally killed, May. 1, two and one-half months after inoculation. None of them showed any lesions and the microscopic sections of the various organs failed to reveal any changes.

The second portion of the nodule was again divided and after flaming the pieces were planted at the bottom of two ascitic glucose-agar tubes. The rest of the bacteriologic work on the case was done by Dr. Coulter, and I am indebted to him for the following facts: After eighteen hours, both of the tubes were clouded. Direct examination and subcultures showed *Bacillus subtilis.* The nodules were at once removed, held within a flame until there was free spattering of fat and the entire surface was shriveled and discolored and then were replanted in ascitic glucose agar. The nodules sank to the bottom of the tube before the medium hardened. The ascitic fluid used in these cultures had been repeatedly tested for sterility. One tube has remained perfectly sterile. One tube showed no growth for two weeks.

On the sixteenth day there were two separate areas of clouding at the bottom of the tube, between the nodule and the glass. Each area was somewhat fan-shaped with the wide portion of the fan directed away from the nodule. Three days later there was very slight if any increase in the areas of clouding. A long sterile pipet was introduced to the bottom of the tube encountering considerable resistance owing to the firmness of the medium. At the very bottom, however, about the nodule, there were found several tenths of a cubic centimeter of slightly turbid fluid. About 0.1 c.c. of this fluid was inoculated into each of three ascitic glucose-agar cultures, one being a surface slant, the other two deep cultures similar to the one from which the fluid was withdrawn. Smears of this fluid showed rather large Gram-positive cocci, mostly in chains of from four to ten, but occasionally arranged as diplococci or tetrads. About the latter there was an indistinct capsule. On the following day the subcultures showed the following:

Surface cultures: Profuse growth, for the most part confluent with very numerous, uniformly distributed, more opaque areas. Growth emulsifies easily. It is not very viscid but strings out slightly when touched with the loop. The medium is not precipitated but the growth has extended between the medium and the glass. The medium was freshly slanted before inoculation so that it was quite moist.

Deep Cultures: Uniformly clouded throughout. No gas bubbles or cracks in the medium. Smears showed organism identical with those in the original culture. Smears from the surface growth showed the cocci smaller, somewhat

flattened and generally arranged as diplococci, chain formation being very slight. Plates were made from all of the cultures. In all there was but one type of colony in twenty-four hours. This was large, 1.5 by 2.5 mm. in diameter, moist, surface convex and glistening, outline smooth and regular, color uniformly grayish, consistency only slightly viscid.

Growth in peptone broth shows a uniform clouding with very slight sedimentation in six hours. In twenty-four hours there is marked sedimentation, but the fluid remains uniformly cloudy. Smears show chains of ten or more cocci with a distinct capsule. The organism is not bile-soluble and shows the following fermentation reactions: Dextrose +, dextrin +, saccharose +, lactose +, galactose +, inulin —, raffinose —, mannite —, salicin +, litmus milk +, acid, coagulated but not dissolved.

Animal inoculations were made from the second generation of deep cultures. An emulsion was made up to the strength of 500,000,000 to the cubic centimeter and of this a guinea-pig received 0.75 c.c. intraperitoneally, a rabbit 1.5 c.c. intravenously and a monkey 1.5 c.c. intravenously. None of these animals showed any reaction. They continued perfectly well and were killed two months later. They showed no gross or microscopic lesions. Another rabbit was given 5 c.c. of an emulsion containing 1,000,000,000 to the cubic centimeter. Death resulted in eighteen hours. The organism was recovered at the necropsy. There were no gross or microscopic lesions of the vessels, especially no signs of inflammation about the vessels or in the perivascular lymphatics.

Pieces of tissue were preserved in alcohol, formaldehyd and Zenker's fluid and sections were stained by various bacterial stains. A careful search was made of many sections for bacteria, without results. In some of the sections, especially those of the pancreas, there were some small bodies resembling cocci, but they could not be differentiated from the numerous particles of chromatin present. A set of sections was also stained by the Levaditi method but with entirely negative results.

The foregoing results have been reported in detail because they represent the most extensive bacteriologic investigations yet made on the disease. The examinations can be considered quite negative with the possible exception of the streptococcus isolated from the cardiac nodule. The occurrence of a *Staphylococcus aureus* in the peritoneal fluid seems to be merely a coincidence. Had it any real relation to the disease, it seems inconceivable that it should not have been obtained from the other cultures both during life and at the necropsy. As the cardiac nodule showed a contamination at the start it is, of course, quite possible that the streptococcus was one likewise. Against this is the fact that the nodule was very thoroughly seared and that the growth did not appear until a considerable period of time had elapsed. Even if this organism did come from the nodule it may have been there merely as an accidental secondary infection. As the occurrence of a streptococcus has been the only moderately constant finding in necropsy cultures of other cases it has seemed important to me to include the cultural characteristics of the one found in this case for the purpose of comparison in case any similar organism is isolated in the future.

The animal inoculations have proved nothing except that the disease was not transmitted to them either by the direct inoculation of material from the nodules or by the streptococus isolated. It is quite possible

that the disease cannot be transmitted to these animals. It would have been interesting to have inoculated stags with material from the nodules, but unfortunately this was not possible.

CASES REPORTED UP TO THE PRESENT TIME

The following is a list of cases of periarteritis nodosa reported up to the present time:

Rokitansky, 1852. Studied microscopically by Eppinger thirty-five years later.
Kussmaul and Maier, 1866.
Zimmerman, 1874.
Chvostek and Weichselbaum, 1877.
P. Meyer, 1878.
Eppinger, 1887. Kundrat's case and microscopic description of Rokitansky's.
Fletcher, 1892. Necropsy by von Kahlden.
von Kahlden, 1894.
Graf, 1896.
Rosenblath, 1897.
Freund, 1899.
Krzyszkowski, 1899.
P. Müller, 1899. Two cases.
Schmorl, 1903.
Ferrari, 1903.
Veszprémi and Jancsó, 1903.
Schreiber, 1904.
Mönckeberg, 1905.
Versé, 1905.
Benedict, 1907.
Oberndorfer, 1907.
Bomhard, 1908. Same case as that reported by Oberndorfer.
Benda, 1908. Two cases.
Dickson, 1908.
J. E. Schmidt, 1908.
Longcope, 1908.
Hart, 1908.
Künne, 1909. Same case as that reported by Hart.
Datnowski, 1909.
Beitzke, 1910. Same case as that reported by Datnowski.
Moriani, 1910.
Cooke, 1911.
Veszprémi, 1912. Two cases.
Lewis, 1912.
Jonas, 1912.
Beattie and Douglas, 1912-13.

REVIEW OF REPORTED CASES

So far as it is possible to decide, the preceding thirty-eight cases are true cases of periarteritis nodosa. Up to the present time it has been impossible to be sure of the diagnosis without a microscopic examination of the lesion. Consequently, a case such as that reported by Sabin cannot be included in this series, although it may well have been an instance of the affection. In order to make the record complete, several of these questionable cases are given at the end of this article. These have either been reported as periarteritis nodosa or have been considered such by some authors.

The following review is based on a study of the preceding thirty-eight cases. It is at once apparent on reading over the reported cases

that many are lacking in important details. The more detailed report of additional cases will be necessary to bring the clinical picture to completeness. There is sufficient material, however, to bring out many facts of interest and to give a clinical picture which will at least aid in the recognition of future cases.

Historical.—In 1852, Rokitansky, in a paper entitled "The Formation of Aneurysms of the Arteries in General, Except the Aorta, and Most of Its Important Primary Branches, with the Further Exception of the Cerebral Arteries,"[2] gave the first complete gross description of the disease. Thirty-five years later, Eppinger studied and described the histologic changes in the arteries of the mesentery in this case. To Kussmaul and Maier, however, must go the credit for the first complete gross and microscopic description of periarteritis nodosa and its recognition as a distinct disease. They reported a case in 1866 as "A hitherto undescribed peculiar disease of the arteries which is accompanied by Bright's disease and a rapidly progressive general paralysis of the muscles,"[3] and proposed the name by which the disease has since been known.

There is some ground for believing that the disease was grossly recognized as early as 1755 by Michaelis and Matani, and in 1810 Pelletan reported very briefly a case in which he counted sixty-three small aneurysms on the various arteries. These reports are too brief, however, to admit of any conclusions as to the true nature of the process. From the time of Kussmaul and Maier's publication to 1899, but eight additional cases were reported, or an average of about one case in four years. Then, as the disease became better known, the number of cases showed a considerable increase, twenty-eight being reported in the following sixteen years. Five of the cases are from the United States and two from Great Britain, nearly all of the rest being from Germany.

Name of the Disease.—As one might expect, several names have been proposed to supplant Kussmaul and Maier's "periarteritis nodosa." Thus we have "multiple aneurysmen" of Meyer, "das congenitale aneurysma" of Eppinger, "arteritis nodosa proliferans" of Fletcher, "polyarteritis acuta nodosa" of Ferrari, "meso-periarteritis" of Hart and "panarteritis," "arteritis nodosa" or "polyarteritis nodosa" of Beitzke, according to the view of the author as to the nature of the process. While it is possible that some of these names are a little more

2. Aneurysmenbildung sämmtlicher Arterien mit Ausnahme der Aorta, und der meisten ansehnlichen primitiven Aeste derselben, ferner mit Ausnahme der Gehirnarterien.

3. Eine bisher nicht beschriebene eigenthümliche Arterienerkrankung die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergtht.

accurate than the one originally used, the disease has come to be known under the title "periarteritis nodosa" and it seems better to continue this name, at least until the etiology of the disease has been established, rather than to introduce confusion by using one or other of the various substitute titles proposed.

Etiology.—The fact that the etiology of periarteritis nodosa is still quite unknown lends added fascination to the study of the disease and emphasizes the desirability of recognition of cases during life in order that complete bacteriologic studies may be carried out. The history of the etiologic views falls into three main groups.

Syphilitic: Influenced by Virchow's opinion, Kussmaul and Maier were inclined to the view that the disease was a syphilitic affection of the arteries. Chvostek and Weichselbaum, Graf, Schmorl and especially Versé have been the chief exponents of this view, while Müller and Benedict have found it impossible to rule out. Many pages have been written upholding and combating syphilis as the causative factor. It would lead too far afield to go into all the arguments. Suffice it to say that the great majority of observers are opposed to the idea even when they limit themselves to purely histologic studies; the Wassermann reaction has been negative in the few cases in which it has been applied; no one has been able to find spirochetes in the lesions; a syphilitic history fails in most of the cases; in only a very few have any other syphilitic lesions been found at necropsy, and a similar, if not identical, disease occurs in stags as pointed out by Lüpke.

Mechanical: While no one seriously considers this view at the present time it is interesting historically. Meyer, in 1878, believed that the disease was due to high blood-pressure rupturing the media, which was either imperfectly formed or later injured by some toxic substance such as alcohol. Nine years later, Eppinger upheld the view of a congenital debility of the internal elastica with rupture. A variation of the mechanical theory is encountered in Ferrari's idea that the lesion is produced by the central or local action of a toxic substance, such as alcohol, causing a paralysis of the smooth muscle-fibers. All of the facts are against these various ideas and it is scarcely worth while to discuss them.

Infectious or Toxic: All observers, with the exception of those above mentioned, believe that periarteritis nodosa is the result of an acute infection, the arterial lesion being caused by bacteria or their toxins. The nature of the infecting agent is still unknown. Cultural investigations during life have been few and yet it is rather striking that in the four cases in which blood-cultures have been taken the results have been quite negative. In Datnowski's case these were repeated three times and the same was true in our second case, the last

blood taken being plated in ascitic glucose-agar. While in no way conclusive, these results would seem to point against any one of the commoner organisms as the causal factor. Anaerobic cultures have not been taken. In our second case, ascitic glucose-agar shake-cultures were made from the heart's blood post mortem, but also with negative results.

Another striking fact is that the examination of sections of the lesions for bacteria has almost uniformly failed to show any organisms. Graf found a few short rods in his sections, but felt that they could not be considered, as the necropsy was done many hours post mortem. Longcope found a few chain cocci in sections from the kidney, but they were not in relation to the nodules.

In only eight cases have cultures been taken at necropsy. In one instance they were accidentally destroyed, leaving the following seven observations:

Oberndorfer: *Staphylococcus aureus* cultivated from the kidney and spleen.

Datnowski: Streptococcus cultivated from the heart's blood. There was a terminal perforative peritonitis in this case.

Veszprémi: Cultures sterile.

Jonas: Streptococcus obtained from the kidney and an influenza bacillus from the adrenal.

Beattie and Douglas: Streptococcus obtained from the renal hemorrhage.

Lamb, Observation I: Streptococcus from the heart's blood associated with a colon bacillus. Streptococcus from the peritoneal exudate. In this case there was a vegetative endocarditis and terminal peritonitis.

Lamb, Observation II: Streptococcus from the cardiac nodule. *Staphylococcus aureus* from the peritoneum and colon bacillus from the pericardial fluid.

Thus, in all but one case in which cultures have been taken, some organism has been obtained. In five of these it was some variety of streptococcus. In two out of these five there was some complicating condition and in two there was also some other organism isolated. In Longcope's case a few chain cocci were found in the kidney sections, but not in association with the nodules.

In reviewing the etiology, one finds no support for the syphilitic or mechanical theory. The course of the disease, the irregular temperature, the high leukocytosis, the complications and the nature of the lesion all point to some infection. Cultures taken during life have been uniformly negative, but have also been limited in number. The failure to demonstrate any bacteria in the lesions may indicate their early

disappearance as is supposed to be the case in rheumatic lesions. While one is not justified in excluding the occasional finding of such an organism as the *Staphylococcus aureus* or influenza bacillus in post-mortem cultures, the most striking point in the examinations so far made is the occurrence of some variety of streptococcus in five of the seven cases, or in 71 per cent. In another case they were seen in sections. It is for this reason that we have included a full description of the streptococcus isolated in our second case. Animal inoculations with this organism and with material from the nodules have been negative.

At present, one can do no more than call attention to these facts as they have occurred. The final solution rests with the future.

It is contended by some that the disease is not specific, but that it is merely an acute infectious lesion of the arteries due to any one of a number of bacteria.

Heredity.—There is no indication that it plays any part.

Sex.—Of the reported cases, twenty-eight were in males, nine in females and in one the sex is not stated. Thus it would appear that the disease is about three times more frequent in males than in females.

Age.—It is essentially a disease of adolescence and early adult life —71 per cent. of the cases occurring between the ages of 10 and 40. It is not limited to this period, however, the youngest case being in a child 2½ months old, and the oldest occurring at the age of 57. The number of cases in the second decade is slightly larger than in any other. The following table shows the number of cases in each decade:

Years	No. of Cases
1-10	1
10-20	10
20-30	8
30-40	9
40-50	5
50-60	5

Occupation.—This is most varied and it is quite impossible to discover any connection with the affection.

Past History.—In about one-third of the cases this is not given. In only four cases is there a definite history of syphilis. In a few there is a history of symptoms similar to but antedating the symptoms of onset by some months or years. In a few there is a history of some immediately preceding infection. There is thus no apparent relation to any other disease, and one gathers the impression that the previous illnesses are entirely irrelevant. It is, however, interesting to note that some cases do show similar symptoms in their past history either as isolated occurrences or in recurring attacks.

Symptoms.—Onset: In the 32 cases in which this is mentioned, we find a more or less acute invasion in 14 cases and a more gradual onset in 18. The symptoms of onset in order of frequency were as follows: Pains in the muscles or joints, 13; fever, 9; abdominal pain, generally in the epigastrium, 8; edema, 8; weakness, 5; disturbances of sensation, 4; diarrhea, sweating, purpuric eruption, sore throat, 3 each; chilliness, headache, vomiting, anorexia, constipation, cough, 2 each; and scattered symptoms of dizziness, urticaria, pain in the chest, eruptions, hemoptysis, cyanosis, dyspnea, icterus, swelling of the testis and asthma.

General: Mentioned in 32 cases. Weakness, generally progressive, 24; emaciation, 13; sweating, 7; jaundice, 6; sleeplessness, 4; chilliness, 4.

Subcutaneous Nodules: In two cases (Schmorl, Benedict) the diagnosis has been made during life by the examination of excised subcutaneous nodules. Everyone has been impressed with the importance of these nodules and it is generally agreed that they offer the only certain means of diagnosis. And yet they were present only eight times or in about 21 per cent. of the cases. In Kussmaul and Maier's case, small, firm, pea-sized nodules appeared beneath the skin of the abdomen and thorax four days before death. Freund merely states that there were subcutaneous nodules of the face, neck and arms noticed during the patient's eight days in the hospital. Müller (Case 1) found the nodules about one knee at the necropsy.

Schmorl reports very briefly the case of a woman who showed nodules in the abdomen and thigh which on excision were characteristic of the disease. They were apparently cured by antisyphilitic treatment. Mönckeberg noticed a few, small, elastic, painless nodules in the thigh on the day before death. Benedict has described the nodules in more detail. At the end of the fourth week, in his case, a fist-sized tumor appeared in the abdomen and increased somewhat in size. This was finally considered an intramuscular hematoma. At about the same time, four or five hazel-nut-sized, round, painless, easily movable nodules appeared in the skin of the thorax and several pea-sized nodules in one leg and in both forearms. A thoracic nodule showed only clotted blood. Later, eleven pea-sized, round or oval, moderately hard, freely movable, nodules were found under the chin and in the buttocks, arms and legs, three hazel-nut-sized tumors under the left breast and a goose-egg-sized nodule containing pus under the left trochanter. A second small nodule removed from the leg showed changes characteristic of the disease. In Datnowski's case there was slight periosteal thickening of the tibia, and four days before death small elevations of the abdomen appeared. It was suggested that both

these represented subcutaneous nodules, but no examination was made. In the first of the cases here reported, there was a peculiar small firm area in the course of the internal saphenous vein, a raised reddish-brown area 3 by 1 cm., in the right thigh, lying over a superficial vein and the early appearing goose-egg-sized hematoma-like swelling of the ankle. These were not in evidence at the necropsy and so, unfortunately, no examination was made.

Superficial Lymph-Nodes: These were noted as enlarged in only four cases.

Edema: The most striking fact in this connection is that in twenty-one, or 61 per cent., of the thirty-four cases in which histories are given, there was edema at some time during the course of the disease. In only two cases is it definitely stated to have been absent. In the eleven remaining cases in which the histories are more or less completely given it is not mentioned and was presumably absent. The edema was generally of the ankles, less often of the face or body.

Skin Eruptions: In seven cases there was an eruption of hemorrhagic character, petechial, purpuric or ecchymotic and at times this was associated with urticaria. In a few instances, such hemorrhagic spots were the first things noticed at the onset of the disease, at other times they appeared during the course, generally in recurring crops. In one case there was an eruption of uncertain character, considered to be that of either syphilis or scarlet fever. In another there was a desquamation of the whole body typical of scarlet fever, but without any known preceding eruption. In one of our cases there was a rather late diffuse erythema of the face and body.

Pains in the Joints: In fifteen cases, or 39 per cent., there were definite joint-pains, often quite severe, usually involving more than one joint and behaving very much like acute rheumatic fever.

Pains in the Muscles: In eighteen cases, or 47 per cent., there were pains in the muscles, generally of the extremities, usually quite severe and described as "tearing." In three cases these pains were associated with distinct muscular atrophy.

Temperature: In four cases no mention is made of the temperature. In two cases it is definitely stated to have been normal, while in the remaining thirty-two there was fever. Thus 94 per cent. of the cases have shown a definitely febrile course. In some, it is merely stated that there was slight fever, in others it is perhaps a little difficult to separate the fever of the disease from that of the complications. In reviewing the cases in which there is more detailed information, it is apparent that the temperature is generally irregular, at times reaching 104 or even 105 F., and at other times being subnormal. It is apt to be of a remittent type, the remissions being accompanied by marked sweating.

There are often periods of several days when the temperature is quite normal.

Circulatory System: Symptoms and physical signs directly referable to the heart and vessels are rather strikingly absent. Thus in our second case in which the coronary arteries were most extensively involved, there were no signs to direct one's attention to the heart until near the end. In 7 cases there was enlargement of the heart, murmurs in 7, dyspnea in 5, cyanosis in 4, precordial pain in 1 and pericarditis in 1.

Blood-Pressure: There is information on this point in only five cases. In Benedict's case it was 140, in Datnowski's 215, in Künne's 77 to 100, in the first of our cases 130 to 165, and in the second 104.

Pulse: In five cases the pulse was not mentioned, and in one it was quite slow. In the remaining thirty-two, or 97 per cent., it was increased in frequency, and in sixteen, or in one-half of the cases in which it was increased, it was more rapid than one would expect from the height of the temperature.

Blood: Anemia is a striking feature of the disease. It is stated definitely as being present in 55 per cent. of the cases and is generally described as being most conspicuous. In only five cases is there any record of a red cell-count or hemoglobin estimation. In these counts the red cells varied from 3,500,000 to 2,800,000, and the hemoglobin from 75 per cent. to 42 per cent. Leukocytosis: Observations have been made on the white cells in only twelve cases. Leukocytosis failed in only one case, that of Dickson, in which there was an associated tuberculosis of the lymph-glands and lungs. In two cases it is simply stated that there was a leukocytosis. In the nine cases in which the figures are given, the count varied from 9,000 to 66,000. The low count was in a case in which other, later counts were as high as 24,000. The count is generally high, between 16,000 and 30,000. In only four cases were differential counts made. Of special interest in this connection is the fact, first mentioned by Datnowski, that the eosinophils are increased. In his case they were 10 per cent. In Lewis' case they were from 22 to 30 per cent., and in our first case from 32 to 58 per cent. In all of these cases the usual causes for eosinophilia were excluded. In our second case they were not increased. It is most important to have more observations on this most interesting point, as it may furnish a most valuable means of diagnosis. It is rather significant that the cellular infiltration of the arterial lesions is generally rich in eosinophils. The polymorphonuclear leukocytes are increased in number. Blood-Cultures: Taken in only four cases and sterile in all. In Datnowski's case they were repeated three times. In our second case, three different cultures were taken and one of these was plated in

ascitic glucose-agar. Wassermann Reaction: Taken in only three cases and negative in two. In our second case one test was positive and one was negative. The first was taken when the temperature was high. We have become very suspicious of the accuracy of positive reactions in the presence of high fever. The second test we believe more reliable, as the temperature was low. In one case a negative reaction was obtained with cadaver blood.

Respiratory System: The respiratory symptoms bear very little relation to the disease with the possible exception of the asthma, which is at times cardiac, and the blood in the sputum. In one of our cases asthma was a most striking feature from the outset, and in one other of the reported cases it was severe. In three cases there has been blood in the sputum. The other symptoms have been the following: cough in 8; pulmonary edema, pneumonia, pain in the chest, 2 each; pleural effusion, emphysema and hemoptysis, 1 each.

Gastro-Intestinal System: A large number of the cases show some symptoms referable to the gastro-intestinal system. In order of frequency they have been the following: Vomiting, 17; anorexia, 9; constipation, 7; diarrhea, alternating with constipation, 5; diarrhea, 4; blood in the stools, 1; *Ascaris lumbricoides*, 1. In the only 3 cases in which gastric analyses were made the free hydrochloric acid was either reduced or entirely absent.

Abdomen: The abdominal symptoms are most important. It is this aspect of the disease which is of interest to the surgeons, for at times the symptoms have been severe enough to persuade one that an acute surgical condition existed. The second case here reported is a striking illustration of this. In seventeen cases, or 50 per cent. of those in which the facts are given, there was abdominal pain. In one-half of these it was located in the epigastrium or upper part of the abdomen. In the rest it was generally diffuse over the whole abdomen. In three cases it was in the region of the kidney. In eight cases the abdominal pain was one of the marked symptoms of onset. The character of the pain is fairly constant. In most cases it comes on in recurring attacks and is severe, colicky or cramp-like. At times it is severe and constant for several days at a time. In a few cases it radiates to the back. It is generally associated with abdominal tenderness and distention. In seven cases the liver was palpable and in four cases the spleen could be felt.

Urogenital System: The lesion affects the small arteries of the kidney in nearly every case. Therefore, the symptoms referable to the kidney are most important. In ten cases no mention is made of the urine. In five cases it is definitely stated that albumin was not present. Often, however, there was only one examination of the urine and the

condition of the kidneys at necropsy suggested that, in some of the cases at least, albumin would have been found had repeated examinations been made. In twenty-three cases, or eighty-two per cent. of those in which the condition of the urine is given, albumin was present, generally in moderate amount, but varying from a faint trace to as high as 6 per cent. In the cases in which repeated examinations were made, the albumin was not always present but showed exacerbations and remissions. It was sometimes present at the onset, clearing up as the patient improved and reappearing later. In other cases it was not present until near the end. In fourteen cases, casts were present. These were generally of the hyaline and granular variety, but occasionally they were epithelial. The amount of the urine was reduced in nine cases and in a like number blood was present. In one case there was a faint trace of sugar found. In one of our cases the phenolphthalein output for two hours was too small to estimate on two occasions. The necropsy showed a very severe glomerulonephritis. In the other case the test was not done. In two cases there was infarction of the vessels of the testis.

Nervous System: The following symptoms were noted: Headache, 6; disturbances of sensation, 6; palsies, 4; convulsions, 4; visual disturbances, 3. In one case in which lumbar puncture was done the spinal fluid was sterile and in one of our cases the urea content was 0.323 per cent. In one of the cases showing visual disturbances a lesion was found in one of the retinal arteries. In the other two cases the retina was not examined post mortem.

Pathology.—The lesions of periarteritis nodosa consist in the peculiar arterial nodules and aneurysms and the changes in the various organs dependent on an insufficient or completely obliterated blood-supply. The larger arteries are not affected, the changes being limited to those of the size of the coronary and smaller. The veins and capillaries have never been found affected. The distribution of the lesions is practically that of the small and medium-sized arteries, that is, any arterial area may be involved. There are certain peculiarities, however, in that the arteries of the brain and spinal cord and the pulmonics are very rarely affected. Changes of the former have been found only four times and of the latter only twice. In some of the cases the central nervous system has not been examined. While the pulmonary arteries almost regularly escape, it is not at all uncommon to find the lesion in the bronchial arteries. The lesion has been found in practically every region of the body, including the retina, arteries to the nerves, the muscles, subcutaneous tissue, spermatic cord, diaphragm, etc. In nearly every case there are lesions in the heart, gastro-intestinal tract and kidneys. In 1905, Mönckeberg gave a table showing the site of the

lesions in all the cases published up to that time. It does not seem necessary to enlarge on this table at present, especially as in many of the cases complete examinations were not made and all of the vascular areas were not investigated. Consequently, a table gives a rather erroneous impression.

Two important facts should be borne in mind. In the first place, in no less than five cases, no changes were noted in the arteries at the necropsy and the disease was not suspected until demonstrated in the sections. It is therefore possible that some cases may be overlooked both clinically and pathologically. That this is not often the case and also that the disease is in reality quite rare is shown by the fact that in a recent review of the sections of all cases of nephritis occurring at the Presbyterian Hospital during the past six years, no case of periarteritis nodosa was found, although the disease was carefully looked for.

In the second place, in five cases, the disease was limited to a relatively small vascular area or to one organ. Some time ago this was used as an argument against such a case being truly periarteritis nodosa, but it is now well recognized that such limitation may occur.

The gross appearance varies somewhat. In most cases there are both solid nodules and aneurysms. These occur with especial frequency at the points of branching, the size of the nodules having no relation to the size of the artery. The nodules are whitish to yellowish-white, moderately firm, later quite firm, and vary in size from those just visible and resembling miliary tubercles to those the size of a pea or slightly larger. They are generally situated at one side of the artery, but at times the whole wall of the artery seems thickened. As indicated above, many of the lesions are quite invisible to the naked eye. On section, they appear homogeneous, yellowish-white, and often show an associated occlusion of the artery. The larger nodules are generally aneurysmal dilatations, are generally softer in consistency and vary from a yellowish-white to a grayish-red or dark-red. These are almost regularly filled with thrombus and may slightly exceed a hazel-nut in size. The aneurysms and nodules may occur together on the same artery and often occur in thickly set bunches or are strung along the branch, giving it a corded or nodular feel. There may be petechial hemorrhages over the lesions and hemorrhagic extravasations into the surrounding tissues. The aneurysms may rupture resulting in hematomata. Quite regularly one finds infarcted areas in some of the organs from occlusion of the arteries at the site of the lesion. The portions of the arteries in which there are no nodules show no changes. The lesion may be quite early in one region and more advanced in another.

Perforation of the intestine may occur through an ulcer caused by infarction.

Microscopic Findings.—One of the chief points of controversy has been the question as to which coat of the artery is the seat of the primary change. The majority of observers believe that the disease begins in the adventitia, a fair proportion are equally insistent that the media represents the primary change. While there have been a few exponents of a primary intimal inflammation, all recent observers are agreed that the process does not begin there. It is believed that the injurious agent probably enters by way of the vasa vasorum or possibly the perivascular lymphatics, and affects one or other of the two outer coats. The reason that there has been so much difference of opinion concerning the relative degree of involvement of the different coats is that the lesion varies considerably in various portions of the same nodule and in the early and late stages of the disease. It is only by the study of serial sections and a review of the various histologic descriptions in the different cases that one can obtain a proper idea of the whole picture. Summing up these changes, we find the picture in the various coats as follows:

Intima: Is frequently not involved. No one has found changes here without simultaneous changes in the other coats. It is on this basis especially that the intima has been ruled out as the site of primary change. As a rule, with the changes in the other coats there is some degree of involvement of the intima. At times there is simply a proliferation of the endothelial cells, at times this is sufficiently marked to cause narrowing of the lumen. The cells then often appear large and polygonal in shape with clear, spindle-shaped or irregular nuclei; the tissue appears vacuolated; there may be some edema and fibrin with an occasional polymorphonuclear leukocyte and wandering cell and some nuclear fragments. A little later fibroblasts appear and with the formation of thrombi these cells grow into and organize the thrombus mass, at times leading to complete fibrous occlusion of the vessel. The changes may affect only a portion of the circumference or the whole intima. The cellular exudate of the media and adventitia may break through the internal elastica and invade the intima. The intimal thickening may extend for some distance beyond the nodule.

Internal Elastica: Generally at the site of the lesion it is wanting. In some cases it is quite sharply broken, the ends tending to curl up; more often it fades away into the exudate of the other coats. Often one can find it quite intact on the other side of the lumen. It may show definite small breaks in continuity in this region. At times it appears distinctly swollen at the site of the nodule.

Homogeneous Hyaline Ring: This is a very characteristic peculiarity of the lesion and consists of a zone of varying width, of more or less homogeneous appearance which takes the eosin stain quite intensely. It is generally situated just external to the internal elastica which is often preserved. In some cases it has been described as lying internal to the elastica and, as mentioned in one of our cases, it may lie both external and internal to it. In the more advanced lesion the band or ring is hyaline and structureless in appearance; but it seems quite possible to trace its formation from the degenerated media. Certainly, in the early stages the inner portion of the media can be seen to be more or less degenerated, its elements fusing together and taking the eosin stain more intensely. At a little later stage one sees the hyaline ring in this location quite distinctly, but it is quite possible to make out the degenerating smooth muscle cells within it.

Media: This coat is almost regularly involved. Mönckeberg even goes so far as to say that when no changes are demonstrable they really exist and that our present means of examination are not delicate enough to make them out. The early changes consist of swelling of the muscle-cells with a loss of their nuclei. One then finds a beginning inflammatory exudate of polymorphonuclear leukocytes, wandering cells and eosinophils, increasing to an extensive similar exudate with some fibrin, edema, nuclear fragments and vacuolization with increasing degeneration of the media, the formation of the hyaline band and later the appearance of fibroblasts and the gradual replacement of the exudate by fibrous tissue. At times, as in the aneurysm formation, the media is greatly thinned. The external elastica shows changes comparable to the internal.

Adventitia: An increasing number of observers have found changes in this coat without the occurrence of recognizable lesions elsewhere in the arterial wall. The earliest change consists of a small periarterial or adventitial collection of mononuclear wandering cells, polymorphonuclear leukocytes and eosinophils. I have been rather impressed with the occurrence of the eosinophils. It has been recognized for a considerable time that they are numerous in the lesions. In our sections, they seem attracted to the region of the arteries even when these show no change. The earliest lesion seen in our sections was in a small arteriole of the stomach-wall. This showed a small unilateral periarterial collection of cells almost all of which were eosinophils. With the older lesions the infiltration of cells increases until the adventitia becomes several times its normal width and merges imperceptibly with the periarterial infiltration which may extend for some distance into the surrounding tissue. The adventitia shows a beginning degeneration and then goes on to the formation of granulation tissue and finally

fibrous tissue. At times one finds the perivascular lymphatics filled with an exudate similar to that described, never, however, to the same extent as seen in such streptococcus infections as erysipelas. The lesions do not go on to suppuration, and in this respect resemble the lesions in the organs in *Streptococcus viridans* endocarditis.

The lesion bears no relation to the supra-arterial epicardial fibroid nodules described among others by Knox. On gross examination these nodules are somewhat suggestive of periarteritis nodosa, but their histologic structure is quite different.

Brief mention has been made above to the occurrence of a similar disease in stags. Lüpke first described this condition in 1906. There has been some divergence of opinion as to the exact relationship between the two conditions. The descriptions of the lesion are rather brief and as we have had no opportunity of seeing sections taken in the cases we feel in no position to judge of their similarity. The consensus of opinion seems to be that the two conditions are very similar if not identical.

Duration.—The most acute case resulted in death in ten days. One case was followed for two years and ten months and was, as far as I have been able to discover, lost sight of at the end of that time. In general, the course is relatively rapid, 71 per cent. of the cases resulting fatally inside of three months. The duration is not always accurately given and in the following table I have considered only the period of acute symptoms.

Duration	No. of Cases
Not given	3
Less than 1 month	5
1-2 months	10
2-3 months	10
3-4 months	5
6-7 months	1
7-8 months	1
8-9 months	1
Over 1 year	2

Prognosis.—This is bad. Only one case in the series did not result fatally. This patient was followed for nearly three years and was alive at the end of that time. One patient in whom the diagnosis was made during life by the examination of an excised nodule was apparently cured of the disease, but died two years later of portal thrombosis. The necropsy showed no evidence of periarteritis nodosa except some small fibroid foci in close relation to the arteries. These were considered healed nodules. Other cases have shown similar but less marked tendency to healing in some regions, but always with progression of the process elsewhere.

Diagnosis.—One need but glance at the following list of diagnoses which have been made in the foregoing cases to obtain some idea of the puzzling nature of the disease: nephritis 7, meningitis 3, general miliary tuberculosis 2, general peritonitis 2, sepsis 2, dysentery, trichiniasis, morbus maculosus Werhlofii, encephalitis, typhoid, polymyositis, polyneuritis, dermatomyositis, cerebral hemorrhage, appendicitis and Schönlein's purpura rheumatica. One thing which one notices about these diagnoses, in reading over the cases, is that they were not considered quite typical and that they did not fully explain the picture.

While some few observers are inclined to the belief that the disease is not a distinct entity, but that it is merely an unusual incident in the course of some acute infectious disease, the majority of those who have studied it clinically and pathologically have come to the conclusion that periarteritis nodosa is a disease *sui generis*. Until the etiology is cleared up this point cannot be definitely determined; but the facts seem to point to the latter point of view.

The difficulty in arriving at a symptom-complex on which a diagnosis may be made lies in the wide-spread distribution of the lesions throughout the arterial system, with the corresponding symptoms in one or more regions or organs. Add to this the tendency of the disease to spread to new vascular areas and the occurrence of numerous overshadowing complications and one can appreciate the difficulties in the way of reaching a correct diagnosis.

Is it, then, possible to construct a symptom-complex of periarteritis nodosa sufficiently definite to make a diagnosis possible? Such a diagnosis has been correctly made only twice during life and then by the excision and examination of the subcutaneous nodules. Barring the presence of these nodules, an answer to the foregoing question must be in the negative. I believe, however, that a consideration of certain symptoms and groups of symptoms should make it possible to suspect the disease and should lead to more careful examinations for subcutaneous nodules. When the disease is once suspected every possible examination should be made to aid in clearing up the etiology. Since the occurrence of the above cases in the hospital, there have been at least two cases in which periarteritis nodosa has been suspected. In both of these there was a purpuric eruption and in both some of the spots were excised for microscopic examination. Neither case turned out to be an instance of this affection.

In practically all of the cases there is fever of a more or less irregular type, rapid pulse, often disproportionately so, anemia and progressive weakness and a striking leukocytosis with a high percentage of polymorphonuclears and in some, at any rate, a distinct eosinophilia. It is most important to have this eosinophilia confirmed by future

observations, for if it be at all constant it will furnish a most valuable means of diagnosis. The above facts stand out clearly and represent a pretty definite background against which one must form the clinical picture. Of almost equal importance, even if not of quite as common occurrence, is the presence of edema and the symptoms of nephritis. While one would, of course, hesitate in making any diagnosis on these symptoms one should be equally reluctant in suspecting periarteritis nodosa without them. If one finds, in addition, some of the following less common but quite frequently present symptoms, it seems justifiable to suspect the disease: pains of tearing character in the extremities; pain and swelling of various joints; attacks of acute abdominal pain, colicky in character and generally located in the upper abdomen; vomiting; hemorrhagic eruptions; cyanosis; asthma. If subcutaneous nodules appear, the diagnosis can be easily settled by excision and histologic examination. In addition it should be remembered that the course of the disease is relatively short and that there may be distinct periods of remission of symptoms and improvement.

OTHER DOUBTFUL CASES

In addition to the list of cases considered in the preceding review, there are a few which have many points in common with periarteritis nodosa and which have been included in reviews of the disease by some authors. Some of them are possibly and even probably instances of this affection, but the failure of histologic examinations makes a decision impossible. The authors of these cases with the dates of publication are the following: Gee, 1871; Thompson, 1877; Sabin, 1901. In addition, there are the cases of Matani, Michaelis and Pelletan already referred to. The cases of Geipel and Eichorst are apparently not cases of this affection.

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The following references to the true cases of periarteritis nodosa are arranged alphabetically:

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Beitzke: Virchows Arch. f. path. Anat., 1910, cxcix, 214; Verhandl. d. deutsch. path. Gesellsch., 1909, xiii, 213.

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Cooke: Proc. Path. Soc., Philadelphia, 1911, New Series, xiv, 96.

Datnowski: Wien. klin. Rundschau, 1911, xxv, 469, 488, 503, 520; Inaug. Diss., Berl., 1909; Ueber Periarteritis nodosa, E. Ebering, Berlin, 1909.

Dickson: Jour. Path. and Bacteriol., 1908, xii, 31.

Eppinger: Arch. f. klin. Chir., 1887, xxxv, Sup., p. 126.

Ferrari: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1903, xxxiv, 350.

Fletcher: Ibid., 1892, xi, 323.

Freund: Deutsch. Arch. f. klin. Med., 1899, lxii, 537.

Graf: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1896, xix, 181.

Hart: Berl. klin. Wchnschr., 1908, xlv, 1305; Veröffentl. d. Hufeland Gesellch., Berlin, 1909, ii, Teil 7-18.
Jonas: Munchen. med. Wchnschr., 1912, dxcii, 1685.
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Moriani: Inst. d'anat. Path., Sienne, 1910; abstr. Arch. d. mal. d. coeur., 1911, iv, 460.
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Rokitansky: Quoted by Eppinger, Denkschr. d. kaiserl. Akad. d. Wissensch., Wien, 1852, iv, 49.
Rosenblath: Ztschr. f. klin. Med., 1897, xxxiii, 547.
Schmidt: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1908, xliii, 455.
Schmorl: Verhandl. d. deutsch. path. Gesellsch., 1903, 203.
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Veszprémi and Jancsó: Beitrage, Ibid., 1903, xxxiv, 1.
Veszprémi: Ibid., 1912, lii, 476.
Von Kahlden: Ibid., 1894, xv, 581.
Zimmermann: Arch. d. Heilk. (Wagner), 1874, xv, 167.

The following is a list of the literature on the other cases mentioned and other articles dealing with the disease:

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Geipel: Munchen. med. Wchnschr., 1907, xx, 1057.
Jaeger: Virchows Arch. f. path. Anat., 1909, cxcvii, 71; XIII, Verhandl. d. deutsch. path. Gesellsch., Leipsic, 1909, 209.
Lüpke: Verhandl. d. deutsch. path. Gesellsch., Stuttgart, 1906, 149.
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Michaelis: Quoted by Eppinger. No reference.
Pelletan: Clin. Chir. on Memoires et observations de chir. clin. et sur d'autres Objects, etc., Paris, 1810, T. I.
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LATENT HYPERTROPHY OF THE HEART IN THE NEPHRITIS OF CHILDREN *

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Ever since Traube established the close relationship between chronic nephritis and cardiac hypertrophy and the recognition of arterial hypertension as the cause of the latter, there has been an increasing tendency to see in a left ventricular hypertrophy presumptive evidence of an underlying chronic nephritis, in the absence of some other cause to explain it.

Whether we follow the school of Romberg, which makes arterial hypertension the consequence of a glomerular lesion, or adhere to the opinion of Jores,[1] that high pressure results from a fibrosis of the smaller vessels, including those of the kidney, it seems agreed that the occurrence of high blood-pressure and its corollary, cardiac hypertrophy, point to a lesion in the vascular component of the kidney.

It is, however, not only in the outspoken cases of nephritis that we expect to find cardiovascular changes. Even in those not uncommon cases of nephritis in which evidences of renal insufficiency and anomalies of the urinary secretion are negligible or absent, heart changes are frequently encountered.

So true is this, that very often, chronic nephritis in adults, in so far as it affects the functions of any organs and the health of the individual, is essentially a cardiovascular disease and death results from heart failure.

While these facts are well recognized in the case of adults, the rôle which cardiac hypertrophy plays in the nephritis of children is not so well known. Various difficulties surround the solution of this question. The nephritis of children is in many cases not a frank one and may be difficult of diagnosis. This is especially true of paedonephritis, a condition the recognition of which we owe to Heubner.[2] He has directed attention to the frequency of very mild cases of chronic nephritis in children, in which the urinary signs may consist only in an albuminuria, at times intermittent, with occasional casts. These signs are easily overlooked in a cursory examination, especially as manifestations of renal inadequacy are frequently absent. To the question, "Does

* Submitted for publication, Jan. 14, 1914.

1. Jores: Deutsch. Arch. f. klin. Med., 1908.
2. Heubner: Jahrb. f. Kinderh., 1913.

cardiac hypertrophy complicate such cases in children?" we can give only a doubtful and clinical answer, because autopsies are rarely available to instruct us, due to the benign character of the disease. We are dependent, therefore, in deciding this question on such aids as clinical examination can afford us. These are, examination of the heart by the usual methods and estimations of the blood-pressure.

To take up the latter first, it must be confessed that the evidence of increased blood-pressure in children is equivocal. In them, the normal variations are considerable and it is a matter of difficulty to decide in the individual case whether the pressure has exceeded its physiological limits. On the other hand, the clinical signs on which we are accustomed to base a diagnosis of hypertrophy of the left ventricle are more determinate. They are as follows: a forcible apical impulse often heaving in character; corresponding to this there is a loud booming first sound of so-called good muscular quality, which may, in pronounced cases, be described as crunching. Occasionally this sound is roughened or split so that it may simulate a short presystolic murmur. There is always an accentuation of the second aortic sound. While these changes in the cardiac physical signs are easily elicited in the larger hearts of adults, in the case of children with moderate grades of hypertrophy they may not be so striking and may be masked by the cardiac overaction consequent on the examination.

The necessity for the determination of these secondary heart changes becomes the greater when it is realized that such information must be of great value in guiding prognosis; for setting aside for the moment the question of cure in mild cases of chronic nephritis, the possibility of complete recovery of the patient will be determined to a great extent by the degree to which the renal injury has compromised the efficiency of the cardiovascular system.

In the solution of this question, the fluoroscope can afford us decisive help. It is well known through the work of Dietlen,[3] Grodel[4] and Otten,[5] among others, that alterations in the mass of the heart and in the volume of its cavities result in typical changes in its morphology, varying with the site of the lesion. Of these changes none is more characteristic than hypertrophy or dilatation of the left ventricle. An increase in the size of this structure whether of mass or volume, causes the left border of heart as seen on the screen to acquire a more or less elliptical curve, its apex becomes blunt and rounded and its axis approaches the horizontal. Very striking is the deliberate, forcible and slow contraction of the left ventricle, of unusual amplitude. Not

3. Dietlen: Deutsch. Arch. f. klin. Med., 1903, No. 88.
4. Groedel: Deutsch. Arch. f. klin. Med., 1908, No. 93.
5. Otten: Deutsch. Arch. f. klin. Med., 1910, No. 105.

uncommonly, under the influence of increased stroke-volume or because the blood is ejected with greater force, the aorta becomes dilated and shows an exaggerated expansile pulsation with each systole (Fig. 1).

The change in the shape of the heart here described occurs irrespective of any increase in its size to percussion and admits of the recognition of slight degrees of hypertrophy, which in many cases must be difficult or altogether impossible by the ordinary methods of examination.

In the application of fluoroscopy to the determination of heart changes in nephritic children, I have studied different varieties of the disease. In some cases, children whose urines on one examination were negative were nevertheless included in the series because they had had scarlet fever with or without acute nephritis and because subjective

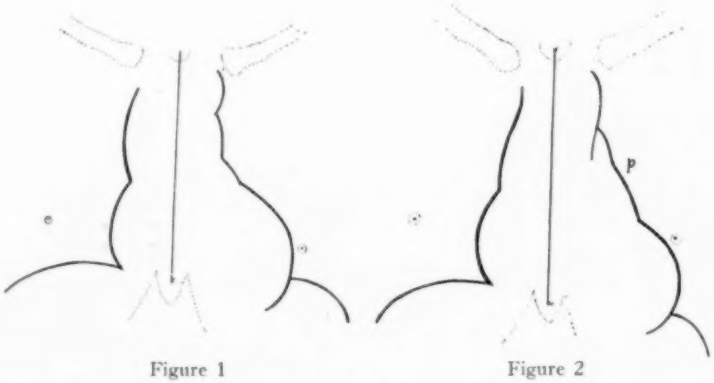

Figure 1 Figure 2

Fig. 1.—Left ventricular hypertrophy.

Fig. 2.—Left ventricular hypertrophy with secondary dilatation; mitralization.

cardiac symptoms suggested the possibility of cardiac involvement. In these cases it was usually possible by the orthodiagraph to demonstrate the characteristic heart appearance above described. I have especially chosen cases in which on physical examination alone, owing to absence of enlargement of the heart and because of the trivial character of the subjective symptoms, cardiac disease was difficult of proof and in which for this reason the help afforded by fluoroscopy was all the more pronounced. In a similar manner, a number of the more severe and outspoken forms of chronic nephritis with marked glomerular lesions was studied; finally a lesser number of acute nephritides was examined to ascertain, if possible, the occurrence of hypertrophy of the heart in this condition.

TABLE 1.—Cases—

Case No.	Age Years	Etiology of Nephritis	Present Nephritic Symptoms	Previous Nephritic Symptoms
1	5	Sarlet fever 3 months ago.	Pale urine; faint trace albumin.	Three months ago general edema; vomiting; albumin, ++.
2	12	Scarlet fever 8 years ago.	Urine negative.	None.
3	11	Scarlet fever years ago.	Pale, pigmentation; headache; albumin, trace.	Headache for some years.
4	14	Measles and diphtheria in childhood.	Pale; puffy eyes; urine: trace of albumin and hyaline casts; bl. pr. 125.	None.
5	10 6/12	Scarlet fever 1 year 8 months ago.	Pale pigmented skin; trace of albumin; hgb., 80 per cent.	For 1 yr. 8 mo. has been pale; headache; persistent albuminuria; no casts.
6	5	Tonsillitis years ago; severe tonsillitis 3 months ago.	Tired; poor appetite; pigmentation of skin; albumin, ++; hyaline casts, sp. gr., 1.012.	One month ago, albumin found in urine.
7	9	None ascertained.	Headache; urine negative.	Ten months ago, general edema; headache; bloody urine (acute nephritis).
8	9	Scarlet fever 8 months ago.	Pale; puffy eyes; urine negative.	Eight months ago, edema and hematuria.

—OF MILD NEPHRITIS

Cardiac Symptoms	Cardiac Signs	Heart Size, cm.		Heart Shape and Action
			Normal	
None.	Forcible apex beat; impure first sound; aortic second accentuated.	Ml. ..... 6.3 Mr. ..... 3.2 Tr. ..... 9.5 L. 9.4	Ml. ..... 5.92 Mr. ..... 2.85 Tr. ..... 8.77 L. 9.3	Hypertrophied left ventricle; aorta wide; slow, deliberate, strong contraction.
.....	Apex, 1 finger outside nipple; forcible apex beat; slow; aortic second accentuated.	Ml. ..... 6.9 Mr. ..... 4.5 Tr. ..... 11.4 L. 12.0	Ml. ..... 7.2 Mr. ..... 3.1 Tr. .....10.3 L. 11.1	Left ventricular hypertrophy; dilated aorta; slow, forcible action.
None.	Heaving apical impulse; faint systolic murmur; accentuated aortic sound.	Ml. ..... 7.0 Mr. ..... 3.1 Tr. .....10.1 L. 9.9	Ml. ..... 6.3 Mr. ..... 3.04 Tr. ..... 9.4 L. 10.1	Hypertrophy with secondary dilatation of left ventricle; mitralization; strong contraction; aorta much dilated.
Palpitation; dyspnea; cough; pallor.	Apical sound booming; split; pseudostenotic murmur; aortic second +.	Ml. ..... 6.9 Mr. ..... 3.0 Tr. ..... 9.9 L. 10.0	Ml. ..... 7.28 Mr. ..... 3.11 Tr. .....10.39 L. 11.1	Typical left ventricular hypertrophy; strong contraction; aorta dilated.
Pale, weak, decompensated, dyspnea; after 2 weeks' treatment no symptoms.	Heart dilated; apex impulse, diffuse, thrusting, apical, systolic murmur, P_2++, A_2+; poor pulse.	Ml. ..... 7.1 Mr. ..... 3.7 Tr. ..... 10.8 2 weeks later Ml. ..... 7.3 Mr. ..... 3.2 Tr. 10.5	Ml. ..... 6.35 Mr. ..... 3.04 Tr. ..... 9.4 L. 10.1	Dilated and hypertrophy of left ventricle; mitralization; poor contraction.
Easily tired; palpitation.	First sound good muscular quality; A_2 ringing.	Ml. ..... 5.6 Mr. ..... 3.2 Tr. ..... 8.8 L. 8.5	Ml. ..... 5.7 Mr. ..... 2.8 Tr. ..... 8.5 L. 9.3	Hypertrophy of left ventricle; deliberate, strong contraction; wide aorta.
Dyspnea and palpitation on exertion.	Forcible apex beat; first sound good muscular quality; A_2 ringing.	Ml. ..... 6.5 Mr. .....4.1 Tr. ..... 10.6 L. 11.0	Ml. ..... 6.79 Mr. ..... 3.08 Tr. ..... 9.8 L. 10.9	Hypertrophy of left ventricle; enlargement to right; forcible pulsation of left ventricle and aorta.
Dyspnea and palpitation on exertion.	First sound impure; basic sounds accentuated; A_2 ringing.	Ml. ..... 6.5 Mr. ..... 3.5 Tr. .....10.0 L. 10.3	Ml. ..... 5.97 Mr. ..... 2.8 Tr. ..... 8.8 L. 9.3	Left ventricle hypertrophied and dilated; mitralization; aorta dilated.

I. CASES OF MILD NEPHRITIS

In this group are included eight cases the findings in which are summarized in Chart 1. A résumé of this shows the following: five had scarlet fever from three months to eight years previously. Five have a history of a previous acute nephritis, which was in all except one of the glomerular type. Five of them at present have mild cardiac symptoms, such as dyspnea on exertion and palpitation. So mild were these complaints that often they were not commented on by the patient and had to be elicited by questioning.

Of these eight cases, five showed albumin in the urine usually in traces, not constantly, and with the occasional appearance of hyaline casts. In three of them, on a single examination, albumin was not found.

The physical signs pointing to cardiac hypertrophy were the classical ones. They were in evidence in each case and especially significant was the clear, and at times ringing aortic second sound, which usually exceeded in intensity the pulmonic sound. This phenomenon, reversing as it does the condition normally found in children, is very striking.

In all the cases in this group the orthodiagraphic examination disclosed a more or less marked hypertrophy of the left ventricle, which was further manifested by a slow deliberate ample contraction of this structure. The aorta was frequently dilated and showed an unusually marked pulsation. It will be observed on comparing the size of the heart with the normal control figures (Veith[6]), that four of them showed a moderate dilatation to the left, too small, however, to be demonstrated by percussion.

There was evidence in two of the patients of a muscular insufficiency of the left ventricle. This gave rise in Case 5 to symptoms of decompensation together with a systolic murmur at the apex and some impurity of the first sound. That this cardiac weakness, with the accompanying murmur, took its origin in a dilatation of a previously hypertrophied ventricle rather than in an organically diseased valve is evident from a study of the orthodiagrams in this case. This murmur also was not present on examination a year before.

Figure 2 is the orthodiagram made Jan. 22, 1913, when the patient was decompensated. The apical impulse was powerful, though diffuse, and both basic sounds were accentuated, the pulmonic more so than the aortic. The systolic murmur was loud and was transmitted to the axilla. The tracing of the heart exhibits a hypertrophy and dilatation of the left ventricle, the left border extending beyond the nipple. The pulmonary artery and the left auricle (p) owing to the regurgitation

6. Veith: Jahrb. f. Kinderh., 1908, No. 68.

from the mitral valve, have also become dilated. The appearance here described differs radically from that seen in mitral insufficiency resulting from imperfect valves, as will be evidenced from a study of Figure 3. The vertical position, the shape of the left ventricle, the increase in size to the right and the smallness of the aorta combine to create a heart silhoutte different from the preceding and just as distinctive. This patient was treated with rest and digitalis for one week with a complete subsidence of all symptoms. At that time on examination, the first sound was clear and the murmur was scarcely audible; the second aortic sound was accentuated and was louder than the pulmonic. The orthodiagram showed the heart to be practically of the same size as previously; the pulmonary artery and the left auricle,

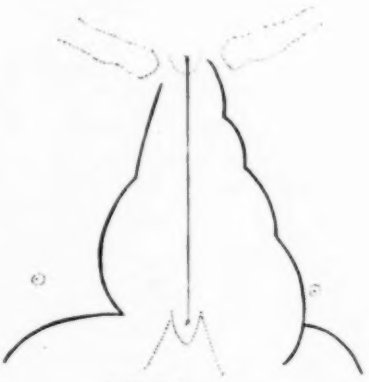

Figure 3

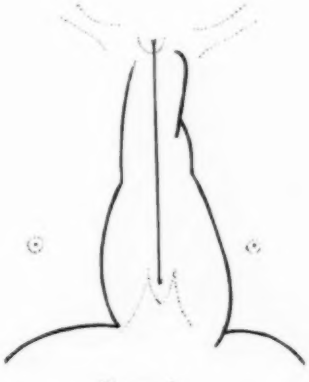

Figure 4

Fig. 3.—Valvular mitral insufficiency.
Fig. 4.—Drop heart.

however, were more prominent, indicating probably a permanent backflow from the ventricle. This condition, so-called mitralization, was present in a few of the cases and confirmed the findings of physical examination.

In this series of cases the absence of urinary evidence in three of the cases of nephritis may be the occasion of some criticism and may be taken as a cause for doubting the existence of an actual nephritis in them. In this regard, it should be stated that only one urinary examination was possible usually; and when it is remembered that cases with mild nephritis may have an albuminuria only intermittently, it is not surprising that it should have been missed on a single test. Two of these three cases, however, are known to have had an acute hemor-

rhagic nephritis, one of them eight and the other ten months previous to this report, a fact which greatly diminishes the importance of the negative urinary finding. In the absence of some other cause to explain the left ventricular hypertrophy, I believe, when due weight is given to

TABLE 2.—Cases of—

Case No.	Years Age	Etiology of Nephritis	Present Nephritic Symptoms	Previous Nephritic Symptoms
1	10	Not ascertained	Pale, puffy face; headache; albumin +; hyaline and granular casts and red cells.	Five weeks ago, acute nephritis; edema, hematuria.
2	2 9/12	Scarlet fever three months ago.	Urine shows hyaline and granular casts and red cells.	Three months ago had acute glomerular nephritis with edema.
3	18	Scarlet fever ten years ago.	Edema of eyes; urine: albumin and casts.	Edema of face eight months; albumin and casts.
4	14	Not ascertained	Pale, puffy face; general edema; albumin, casts and red blood cells; bl. pr. 130.	Similar symptoms months ago.
5	16	Scarlet fever thirteen years ago.	Pale; urine: albumin ++, many hyaline and granular casts; red cells; edema of face and feet.	Similar symptoms for 7 weeks.
6	7	Measles (?)	General edema; albumin +++; hyaline and granular casts and red cells.	Eleven weeks ago headache and edema up to present.

the etiology, that a diagnosis of a latent nephritis in these cases has at least a presumptive basis. It is precisely because the fluoroscope is capable of disclosing a typical change in the configuration of the heart that it is of value, as from it we are permitted to infer the presence of a renal lesion, which at the moment is producing no anomaly in the

urinary secretion. An analogy may be seen in the condition of presclerosis of adults in whom the rise of blood-pressure may be insignificant and the urinary changes at times absent, but in whom Pal could usually demonstrate a cardiac hypertrophy.

—Severe Nephritis

Cardiac Symptoms	Cardiac Signs	Heart Size, cm.		Heart Shape and Action
			Normal	
Palpitation and dyspnea on exertion.	Apex outside nipple; first sound impure; strong impulse; A_2++; thick arteries.	Ml. ..... 7.7 Mr. ..... 2.8 Tr. .....10.5 L. 10.0	Ml. ..... 5.97 Mr. ..... 2.8 Tr. ..... 8.2 L. 9.3	Normal action; heart dilated to left; no distinct evidence of hypertrophy.
None.	First sound accentuated; A_2 accentuated.	Ml. ..... 4.5 Mr. ..... 3.1 Tr. ..... 7.6 L. 7.2	Ml. ..... 5.4 Mr. ..... 2.2 Tr. .....7.6 L. 8.6	Forcible action; left ventricular hypertrophy.
None.	Evidence of hypertrophy of left ventricle.	Ml. ..... 8.4 Mr. ..... 4.6 Tr. .....13.0 L. 12.5	Ml. ..... 8.0 Mr. ..... 3.8 Tr. .....11.8 L. 13.0	Typical hypertrophy of left ventricle with slight dilatation.
None.	Left ventricular hypertrophy; split first sound; pseudo mitral stenosis.	Ml. ..... 9.1 Mr. ..... 3.9 Tr. .....13.0 L. 12.7	Ml. ..... 7.28 Mr. ..... 3.1 Tr. .....10.39 L. 11.8	Hypertrophy and dilatation of left ventricle; aorta dilated; forcible action.
Dyspnea and palpitation on exertion.	First sound booming; A_2 + + +; bl. pr. 130; forcible impulse.	Ml. ..... 8.2 Mr. ..... 4.5 Tr. .....12.7 L. 12.7	Ml. ..... 7.9 Mr. ..... 4.3 Tr. .....12.4 L. 13.1	Action, forcible, deliberate; hypertrophied left ventricle.
None.	First sound booming; basic sounds, especially aortic accentuated.	Ml. ..... 5.9 Mr. ..... 2.8 Tr. ..... 8.7 L. 9.3	Ml. ..... 5.7 Mr. ..... 2.8 Tr. ..... 8.5 L. 9.3	Shape of hypertrophy; aorta wide and shows marked pulsation.

II. CASES OF SEVERE NEPHRITIS

This group comprises six cases of chronic and subacute hemorrhagic nephritis in children (Chart 2). The etiology in three of these was scarlet fever; it was undetermined in the others. With one exception, these patients had an acute hemorrhagic nephritis with edema, a rela-

tively short time previously, signs of which continued with abated severity to the present. The urines of all of them contain large amounts of albumin, hyaline and granular casts and red blood-cells. Of cardiac symptoms, these patients had few, only two of them complaining of dyspnea on exertion. The physical signs were uniformly those of hypertrophy of the left ventricle without dilatation, findings which were convincingly shown by orthodiagraphic tracings. These in every case showed the typical appearance I have described, associated with some aortic dilatation. It should be stated that the blood-pressure readings were not sufficiently elevated to permit any deductions to be made from them.

TABLE 3.—CASES OF—

Case No.	Age Years	Etiology of Nephritis	Present Nephritic Symptoms	Previous Nephritic Symptoms
1	9	Tonsillitis 4 days ago.	Edema of face and legs; albumin ++; casts and red cells.	.....
2	16	Severe tonsillitis 4 weeks ago.	Pale, general edema, ascites; albumin ++; casts and red cells.	Ten days ago got edema, headache, vomiting, oliguria.
3	14	Tonsillitis 4 weeks ago.	Pale, general edema; hydrothorax; albumin ++; casts and red cells; bl. pr. 164.	Three and one-half weeks ago had hematuria; vomited.

III. ACUTE GLOMERULAR NEPHRITIS

This group comprises three cases of acute nephritis occurring in children, with a duration at the time of the examination of four days in the first, ten days in the second and four weeks in the third, and caused in each case by an acute tonsillitis. Apparently, in the first case, sufficient time had not elapsed for the production of any alteration in the circulation, for neither physical signs nor the fluoroscope reveal any deviation from the normal. In the two remaining cases an exquisite left ventricular hypertrophy had developed with the usual clinical signs and fluoroscopic appearance.

It will thus appear that as early as the tenth day and the fourth week after the onset of an acute nephritis, the heart is already hyper-

trophied. That this is so should not be surprising when it is recalled that Butterman found a rise in blood-pressure as early as forty-eight hours after the beginning of a nephritis, and that "in primary nephritis the rise in blood-pressure is rarely missed" (Krehl[7]). It is natural to conceive that a hypertension lasting four weeks with the increased work this entails on the heart, should, after the manner of muscular tissues elsewhere in the body, lead to hypertrophy from overwork.

It should be emphasized that we are here not dealing with a simple dilatation of the heart, dependent on a myocarditis such as might be assumed to be present in a weakened and edematous patient. To make this more evident, in Case 2 the patient was examined on two occasions.

—Acute Nephritis

Cardiac Symptoms	Cardiac Signs	Heart Size, cm.		Heart Shape and Action
			Normal	
None.	None.	Ml. ..... 5.8 Mr. ..... 3.7 Tr. ..... 9.5 L. 9.7	Ml. ..... 6.35 Mr. ..... 3.06 Tr. ..... 9.4 L. 10.1	Normal shape and action.
Palpitation on exertion.	Diffuse, forcible apex beat; first sound, booming; A_2++; bl. pr. 155.	Ml. ..... 7.8 Mr. ..... 5.8 Tr. .....13.6 L. 13.4	Ml. ..... 7.9 Mr. ..... 4.3 Tr. .....12.1 L. 13.1	Left ventricular hypertrophy; enlargement to the right.
None.	First sound booming; A_2+.	Ml. ..... 7.8 Mr. ..... 3.5 Tr. .....11.3 L. 12.0	Ml. ..... 7.28 Mr. ..... 3.1 Tr. .....10.39 L. 11.8	Left ventricular hypertrophy; slight enlargement to right; forcible action.

At the first examination ten days after the onset of the nephritis, there were generalized edema, a diffuse though powerful apical impulse and accentuation of both basic sounds. The orthodiagram at this time showed a hypertrophy of the left ventricle; in addition, enlargement of the pulmonary artery and increase of the heart diameter to the right. There was no systolic murmur, and these secondary changes may be looked on as caused by a muscular insufficiency of the left ventricle with a resulting mitralization. Two and one-half weeks later the urine had to a great extent cleared up, the edema had subsided and the patient felt quite well. The examination of the heart nevertheless disclosed outspoken signs of hypertrophy. The muscular weakness of

7. Krehl: Nothnagel's System, 1912, xv.

the left ventricle, however, had mostly disappeared; the heart was less enlarged to the right and the pulmonary artery was much diminished in size.

I have attempted to show in a series of cases of acute and chronic nephritis in children that it was possible to demonstrate in most of them the presence of heart changes, which consist in a hypertrophy of the left ventricle associated at times with slight degrees of dilatation and in a few cases with evidences of enlargement of the right side of the heart. That such changes should occur in the outspoken cases of nephritis with edema and glomerular inflammation, though only weeks or months have elapsed, is perhaps to be expected; one may hesitate, however, in those cases of nephritis in which the urinary findings are often ambiguous and in which, therefore, one may assume the existence of only slight damage to the kidney, to believe that the structure of the heart has suffered alterations capable of recognition — alterations which in their importance overshadow the renal lesion.

The force of this objection is mitigated by the fact emphasized by Jores and Fisher[8] that there is not necessarily a quantitative relation between the degree of kidney disease and the degree of cardiac hypertrophy; similarly Pal,[9] in the presclerosis of Huchard, on autopsy found well developed cardiac hypertrophy, where only a slight grade of kidney inflammation was in evidence.

The frequent occurrence of scarlet fever in the cases here reported is in accord with what is well known in regard to the rôle which this disease plays in the causation of nephritis. All observers are not agreed, however, as to the frequency with which scarlet fever is responsible for chronic nephritis, especially of the milder forms. Thus Escherich and Schick[10] are inclined to doubt the frequent connection of scarlet fever with chronic nephritis. Rosenfeld,[11] on examining forty-one cases of scarlatinal nephritis at intervals of one to ten years, found an albuminuria which was spontaneous or orthostatic, associated in seven cases with casts. Stroink[12] believes that many contracted kidneys in young adults take their origin in an acute scarlatinal nephritis with a long intervening albuminuria, which is easily overlooked.

Heubner, especially, has associated scarlet fever with the milder forms of chronic nephritis in children. According to him, these patients go on for years with minor urinary signs; either they improve

8. Fischer: Deutsch. Arch. f. klin. Med., 1911, No. 109.
9. Pal: Med. Klin., 1909.
10. Escherich and Schick: Nothnagel's System, Supplement, p. 143.
11. Rosenfeld: Ztschr. f. Kinderh., 1912.
12. Stroink: Jahrb. f. Kinderh., 1911.

at the time of puberty, which seems to have a favorable influence on the nephritis, or they go on to contraction in later years.

There seems to be less agreement as to the heart changes which may be a sequel of nephritis and scarlet fever. During the acute stage of scarlet fever according to Lederer and Stolte, evidences of heart-changes are present in as many as 70 per cent. of the cases. Friedlander,[13] in children who died of post-scarlatinal nephritis, found a distinct cardiac hypertrophy in nearly all cases, dependent apparently on the nephritis. Sörenson[14] similarly found a hypertrophy in acute nephritis. Baginski,[15] on the other hand, by clinical methods, found no evidence of cardiac hypertrophy in the acute nephritis of children. In the chronic albuminurias after scarlet fever, however, Rosenfeld rarely found heart-changes. A similar observation occurs in the reports of Stroink and Heubner. There is, nevertheless, *a priori,* reason to suppose that in at least some of these cases the conditions making for cardiac hypertrophy are operative. If it is true that a short time after the onset of an acute nephritis, the blood-pressure already shows an appreciable rise, with presumably its concomitant effect on the cardiac musculature, it is plausible to assume that a similar, though less severe kidney disturbance, will after being operative for months or years, give rise to analogous changes in heart structure.

In the decision of this question, as I have endeavored to show, the orthodiagram is of considerable help in that it supplies objective proof to support physical signs which ordinarily might leave us in doubt. This is especially of value in cases of orthostatic albuminuria, in which for a long time one may be unable to decide whether there is really a nephritis present or only a functional or postural albuminuria exists. Now in orthostatic albuminuria of children, subjective cardiac symptoms are at least as frequent as in the milder forms of chronic nephritis. In addition, in many cases, there are distinct evidences of cardiac overaction and relative cardiac insufficiency, to which such terms as "growth hypertrophy," "juvenile heart" and "dilatative heart weakness" have been applied.

Bass and Wessler,[16] in a study of a series of such cases have noted the great frequency of the asthenic type of heart, the so-called "drop-heart." Such hearts frequently give the clinical signs of hypertrophy; on orthodiagraphic examination, however, they are found, as a matter of fact, to be smaller than normal and present a unique appearance quite different from a heart of hypertrophy (Fig. 4).

13. Friedlander: Arch. f. Anat. u. Physiol., 1881.
14. Sörenson: Ztschr. f. klin. Med., 1891.
15. Baginski: Arch. f. Kinderh., 1902, No. 33.
16. Bass and Wessler: The Archives Int. Med., 1913, No. 11.

It will thus be seen that the presence of such a "drop-heart" in a case of albuminuria will favor the diagnosis of a functional condition and will justify a brighter prognosis; on the other hand, the finding of a left ventricular hypertrophy associated with an albuminuria will afford a basis for a diagnosis of an organic kidney disease.

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THE NON-SPECIFICITY OF CARBOHYDRATE TOLERANCE TESTS *

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About three years ago we commenced using carbohydrate tolerance tests as a routine procedure in all cases in which there might exist a functional disturbance of any of the ductless glands. At that time we thought that if the test were carefully worked out in a large enough series of cases, some diagnostic importance might be attached to it. From a knowledge of the work of previous investigators, we realized that sugar tolerance could never be a specific test, for at least in the metabolism of glucose many organs play a rôle. Von Noorden's[1] conception of the liver as the central figure in a circle of pressor and depressor influences seemed a logical working basis — hypophysis, thyroid and adrenal being pressors, and pancreas the depressor of carbohydrate metabolism. Clinical evidence was forthcoming to show that states of hyperacidity of the pressor organs and hypo-activity of the depressors are often associated with spontaneous glycosuria, or at least a lowered threshold for carbohydrates, whereas in hypo-activity of the pressors the tolerance for carbohydrates is increased.

Strauss'[2] levulose test for hepatic insufficiency, which was based on Sachs'[3] experiments with dehepatized frogs, had been hammered from all sides, with results which could only be classed as discordant. At the time we commenced our tests we thought that there were many factors to account for this, among which may be mentioned:

1. Lack of standard technic.
2. The difficulty of knowing what is meant by "hepatic insufficiency."
3. The probability that other organs played an important rôle in the utilization or non-utilization of sugars employed in the test.

After our actual work was finished, but before this article was written, appeared the excellent article by Bloomfield and Hurwitz[4]

* Submitted for publication May 24, 1914.

* From the Department of Clinical Research, The Michael Reese Hospital, Chicago.

1. Von Noorden: Med. Klinik, 1911, vii, 1.
2. Strauss: Deutsch. med. Wchnschr., 1901, xxvii, 757.
3. Sachs: Ztschr. f. klin. Med., 1899, xxxviii, 87.
4. Bloomfield, A. L., and Hurwitz, S. H.: Tests for Hepatic Function: Clinical Use of the Carbohydrates, Johns Hopkins Hosp. Bull., 1913, xxiv, 375. Full review of the literature.

on the clinical use of carbohydrates as tests for hepatic function. These authors review critically the literature, discuss the theoretical basis for the application of sugar tolerance, and come to the conclusion that the inconclusive experience of others might be expected because "the theoretical basis for the use of sugars as tests for hepatic function is definitely deficient." From a practical standpoint, they maintain that difficulties must arise from (*a*) the method of administration; (*b*) faulty absorption; (*c*) portal obstruction; (*d*) retention of sugars in renal disturbances, and (*e*) the variable amounts of carbohydrate in the diet. A part of the summary of their work is worth quoting verbatim:

> A consideration of the extrahepatic factors involved in the sugar-regulating metabolism, the influence of the glands of internal secretion and of the vegetative nervous system, the ability of other tissues than the liver to handle sugar, and the ability of the uninjured liver substance to compensate in disease, make the sugars theoretically unsatisfactory as tests for hepatic insufficiency.
>
> There are serious objections to the methods as they have been applied, namely, the use of arbitrary amounts of sugar, and the use of a definite standard of excretion.

The main point we attempted to investigate was the relation between sugar tolerance and various clinical states involving one or more than one of the ductless glands. The first great practical difficulty was in the standardization of technic. How much sugar should be given? Is a quantitative determination of the amount excreted necessary? To adopt an arbitrary amount of sugar as a test for all individuals is obviously not a logical procedure, nor can the body weight be considered more logical as a standard of efficiency of sugar metabolism. Apparently the only scientific method is, as Bloomfield and Hurwitz point out, the impossible one of testing the tolerance before and after the disease has started. The practical solution was a compromise: If most normals do not excrete sugar on 100 gm. dextrose and do excrete sugar on 125 gm., then we may fix 100 gm. as the "normal" threshold of sugar tolerance. In our series of approximately 225 tests we included many normals, and as an arbitrary standard we generally started with 100 gm. dextrose, or 90 gm. levulose. The difficulties of administration were easily overcome with the smaller doses by embodying the sugar in 250 c.c. of *sour* lemonade given early in the morning, on an empty stomach. When the doses were larger we occasionally encountered nausea and vomiting, which naturally spoiled the test. In almost every case both dextrose and levulose were administered with *one* day intervening, and only in exceptional cases in which haste was demanded were the sugars given on succeeding days. The urine was collected just before the sugar was given, and at three intervals of two hours

each after the administration of the sugar. Qualitative tests only were employed. When dextrose was given, reduction of Fehling's in a urine negative before the test was called "positive." With levulose we also used the Seliwanoff[5] resorcin test.

We had hoped that by careful determination of the sugar threshold we might receive some aid in the quantitative estimation of the extent of the particular functional disturbance we were studying, but such a procedure unhappily was impossible, because of the practically complete absence of any other quantitative standard of functional deficiency. A clinically mild hyperthyroidism, for instance, might show a markedly reduced sugar tolerance, whereas some of the severest cases gave only a slightly lowered tolerance.

As might be *a priori* expected, the interpretation of results in a scientific manner has been exceedingly difficult. Undoubtedly, the greatest trouble arises from the present state of obscurity surrounding the functions of the various glands of internal secretion. If in a case of suspected hyperpituitarism we could assume that a positive tolerance test meant hyperactivity of the hypophysis, we might prove almost anything by our results, but such a deduction is clearly arguing in a circle and only obscures the further elucidation of a difficult problem. If, on the other hand, we had incontrovertible proof that the suspected condition actually existed, then we would be safe in interpreting our result, according to the suspicion. But unfortunately absolute clinical or anatomical proof in most cases is an impossibility. Therefore, it were the better part of wisdom to consider our results from an ultraconservative point of view, and not attempt to draw any sweeping conclusions, even when the experience of a certain series would seem to point a given way. In many of our cases there can be no doubt that the test has been of distinct individual diagnostic benefit, just as a leukopenia may be of distinct benefit in suggesting *Bacillus typhosus* as the cause of an obscure fever; but we must insist on the distinction between a specific group reaction, and an occasional individual reaction in that group.

Probably the most logical method of presenting our results is by analyzing the various "group reactions." It is impossible in such a large series to go into detail in the different cases, tempting as such a pursuit might be.

The table is merely a summary of the work and includes only those cases in which the diagnosis was apparently certain. The positive dextrose tests are based on a dosage of 100 or 125 gm., while most of the levulose tests were made with 90 gm. The larger per-

5. Strouse and Friedman: Levulosuria, with a Report of an Unusual Case, THE ARCHIVES INT. MED., 1912, ix, 99.

centage of "positives" with levulose in almost all the group headings indicates clearly the well-known lower tolerance of the human organism for levulose.

The forty-eight tests on miscellaneous liver conditions add nothing new to what is already known of the tests in so-called "hepatic insufficiency," and show clearly enough that a conception of the term can not be defined on a basis of carbohydrate tolerance. The apparently sharp differentiation in the results of the tests in thyroid disturbance is much more striking, and is probably due to the more definite understanding of the clinical states of hyper- and hypo-activity of this gland. Possibly we should have been more specific

GROUP REACTIONS

Group	Levulose		Dextrose		Total
	Number	Per cent. Positive	Number	Per cent. Positive	
Liver—					
Cirrhosis	8	12.5	10	70	18
Cholecystitis Pancreatitis ..	6	66.6	2	100	8
Carcinoma liver and pancreas.	2	100	2	100	4
Catarrhal jaundice	4	50	4	50	8
Thyroid—					
Simple goiter...	5	0	3	0	8
Hyperthyroidism	18	50	11	63.5	29
Hypothyroidism.	3	0	..	..	3
Hypophysis	7	43	3	67	10
Pluriglandular ...	7	58	5	20	12
Neurasthenia	33	12	14	28	47
Miscellaneous	30	10	17	35	47

in the classification of our cases of hypophyseal disease, but we do not feel that the present state of knowledge warrants a sharp line between hyper- and hypo-activity in individual cases, and the attempt to draw the line in carbohydrate work would only obscure the problem. The pluriglandular syndromes are interesting and perhaps significant in that they are the only group in the list showing more positive dextrose than levulose tests. As for the "neurasthenia" group, who can tell the mystery into which we grope? Probably many of the neurasthenias of to-day will be functional gland disturbances of the future, but it would be misguided science and erroneous logic to use carbohydrate tolerance as at present understood as a means of classification. The miscellaneous group includes all sorts

of diseases seen in a hospital for acute diseases, and the same commentary might be made here as was just made on the neurasthenia group.

CONCLUSION

From this clinical study we feel justified in stating that whereas tests for carbohydrate tolerance, when grouped as we have grouped our results, may indicate in a general way functional disability of an organ under suspicion, the tests can never be interpreted in an absolutely specific manner. The possibility of the implication of other organs must always be borne in mind. Functional inefficiency of one gland sufficient to lower the threshold of carbohydrate metabolism may be entirely compensated for by functional hyperactivity of a correlated gland. Even in apparently clean-cut individual cases the tests do not follow the course one might logically expect, and therefore in doubtful cases their value must remain very limited.

It gives us extreme pleasure to express our gratitude to the attending and house staffs of The Michael Reese Hospital for courtesies and assistance extended to us in the course of this study.

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THE POTASSIUM CONTENT OF CEREBROSPINAL FLUID IN VARIOUS DISEASES *

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It is now well recognized that certain inorganic ions play a most important part in the proper functioning of cells. Through the researches of Macallum[1] and Macdonald[2] it is known that potassium is present in the nerve-fibers and not in the nerve-cells, and that it was not until some change had taken place in the axis cylinder that potassium was liberated in an ionic state. It might be true, therefore, on the basis of these observations that in any disease with changes in the axis cylinders we might expect to find that the cerebrospinal fluid contained an increased amount of potassium.

Rosenheim[3] asserted that in all cases of acute degenerative insanity in which the presence of cholin was demonstrated in the cerebrospinal fluid, potassium in relatively large amounts could, also, be found; but in the cases in which cholin was absent, very little potassium was found. Myers[4] has shown, however, that the increased potassium content is better explained on the basis of post-mortem changes in the fluid rather than the degenerative changes found in dementia paralytica, and, also, that results obtained with post-mortem fluid cannot be compared with fluid obtained during life. He found little variation in the amount of potassium during life, but after death the potassium content was always increased about four times. Salkowski thinks that the potassium is high in acute cases and low in chronic cases.

In the literature one finds that almost all of the estimations of potassium in cerebrospinal fluid have been carried out on the centrifugated fluid; and as potassium is found in considerable amounts in the blood-cells, it seemed to us better to use fluid that was not centrifuged for the estimations. This is important, also, on account of the rapid cytolysis of the formed elements of this fluid. We also carried out the estimations soon after the fluid was removed, and on account of the rapid post-mortem increase in the potassium content, the fluid in all cases was obtained during the life of the patient.

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* Submitted for publication, May 19, 1914.

* From the Biochemical and Pathological Laboratories of the Western Pennsylvania Hospital.

1. Macallum: Jour. Physiol., 1905, xxxii, 125.
2. Macdonald: Proc. Roy. Soc., 1905, lxxvi, B, 329. Macdonald and Finch: Jour. Physiol., 1907, xxxv, 38.
3. Rosenheim: Jour. Physiol., 1907, xxxv, 465.
4. Myers: Jour. Biol. Chem., 1909, vi, 115.

Ziveri[5] reports that he has found potassium constantly in the cerebrospinal fluid from fifteen epileptics. As it is constantly present in normal fluid, however, it is difficult to see what inference could be drawn from this observation.

The potassium was estimated by the sodium cobalt-nitrite method of Drushel[6] as modified by Myers. In Tables 1, 2 and 3 we have summarized all the potassium estimations in cerebrospinal fluid that have been published.

TABLE 1.—LIST OF ESTIMATIONS FROM THE LITERATURE

Investigator	K_2O in 10 c.c. Fluid mg.	Source of Fluid
C. Schmidt[1]	14.3	Acute hydrocephalus
C. Schmidt[1]	10.4	Acute hydrocephalus
Coriat[2]	8.3	Hydrocephalus
Hilger[3]	6.9	Chronic hydrocephalus
Salkowski[4]	3.6	Chronic hydrocephalus
Panzer[5]	3.0	Hydrocephalus
C. Schmidt[1]	2.7	Chronic hydrocephalus
Nawratski[6]	2.4	Calf
Nawratski[6]	1.9	Calf
Yvon[7]	2.1	Chronic hydrocephalus
Halliburton[8]	1.8	Chronic hydrocephalus
Zdarek[9]	1.7	Meningocele
Mestrezat[10]	3.7	Hydrocephalus
Mestrezat[11]	2.5	Mixture of twenty normal cerebrospinal fluids
Stscherbakoff	10.8	Spina bifida

1. Schmidt: Physiol. Chem. (Hoppe-Seyler's), 1881, 604.
2. Coriat: Am. Jour. Physiol., 1903, x, 111.
3. Hilger: Centralbl. f. d. med. Wissensch., 1867, No. 56.
4. Salkowski: Festschr. f. M. Jaffe, 1901, p. 263.
5. Panzer: Wien. klin. Wchnschr., 1899, xii, 805.
6. Nawratski: Ztschr. f. physiol. Chem., 1897, xxiii, 532; Arch. f. Anat. u. Physiol., 1897, p. 156.
7. Yvon: Jour. de pharm. et chim., 1877, Series 4, xxvi, 240.
8. Halliburton: Jour. Physiol., 1889, x, 232.
9. Zdarek: Ztschr. f. physiol. Chem., 1902, xxxv, 201.
10. Mestrezat: Bull. Soc. chim., 1911, ix, 683.
11. Mestrezat: Jour. de pharm. et chim., 1909, xxix, 472.

Table 4 contains the results obtained in this study as to the potassium content of *uncentrifuged* cerebrospinal fluid obtained *during life*. We also thought it would be of interest to compare the amount of potassium found with the globulin reaction and with the cell-count.

5. Ziveri: Zentralbl. f. Biochem., 1909, viii, 198.
6. Drushel: Am. Jour. Sc., 1907, xxiv, 433; ibid., 1908, xxvi, 555; Ztschr. f. anorgan. Chem., 1907, lvi, 223; 1909, lxi, 137.

TABLE 2.—Potassium Content of Cerebrospinal Fluid Obtained after Death*

Diagnosis	K_2O in 10 c.c. Fluid mg.
Dementia paralytica	11.9
Dementia paralytica	6.9
Senile dementia	7.8
Imbecility	9.3
Dementia praecox	8.6
Dementia paralytica	8.4
Dementia paralytica	11.9
Dementia paralytica	12.0
Dementia paralytica	9.7
Dementia paralytica	8.3
Epilepsy	7.0
Alcoholic delusional insanity	12.7
Alcoholic delusional insanity	10.3
Senile dementia	9.9
Senile dementia	10.6
Senile dementia	12.2
Senile dementia	8.7
Organic dementia	7.2
Melancholia	10.7
Maniac depressive insanity	10.7
Dementia praecox	7.0
Dementia praecox	9.7

* Myers: Jour. Biol. Chem., 1909, vi, 115.

TABLE 3.—Potassium Content of Cerebrospinal Fluid Obtained During Life*

Diagnosis	K_2O in 10 c.c. Fluid mg.
Dementia paralytica	2.2
Dementia paralytica	2.8†
	3.4
Dementia paralytica	2.1
Dementia paralytica	1.8
Dementia paralytica	2.0
Dementia paralytica	1.8†
	2.2
Dementia paralytica	1.7
Dementia paralytica	3.3
Dementia paralytica	3.0
Dementia paralytica	2.3
Dementia paralytica	2.1
Epileptic insanity	1.7
Epileptic insanity	2.2
Alcoholic pseudoparesis	2.1
Korsakoff's psychosis	2.5

* Myers: Jour. Biol. Chem., 1909, vi, 115.
† Estimations made on different days.

TABLE 4.—List of Estimations Carried Out by the Authors

Diagnosis	K_2O in 10 c.c. Fluid mg.	Cell-Count		Globulin Test
		Leukocytes	Erythrocytes	
Normal	6.1	2	0	—
Normal	5.2	1	0	—
Normal	3.6	1	Few	—
Dementia praecox	4.4	67	Occasional	+
Dementia praecox	4.6	2.5	0	—
Dementia praecox	3.4	129	572	+
Dementia praecox	5.0	1	.....	—
Dementia praecox	2.2	17	.....	—
General paresis	1.7	28.5	.....	+
General paresis	3.0	20	0	+
General paresis	6.2	6.5	0	+
Cerebrospinal lues	9.1	9.5	0	+
Cerebrospinal lues	2.4	1	0	+
Cerebrospinal lues	7.3	7.5	.....	+
Cerebrospinal lues	4.1	56	.....	+
Cerebrospinal lues	3.8	5	.....	—
Cerebrospinal lues	8.1	13	0	—
Cerebrospinal lues	5.4	31	Several	+
Cerebrospinal lues	5.2	58	0	+
Chronic alcoholism	1.8	1.5	0	—
Acute alcoholism	8.6	1	0	—
Acute alcoholism	3.2	3	0	—
Presenile dementia	8.6	1	0	—
Encephalitis	3.3	2	0	+
Tuberculous meningitis	5.3	214	0	+
Tuberculous meningitis	5.7	42	0	+
Meningitis	18.3	648	0	±
Neurasthenia	2.5	2	0	—
Neurasthenia	5.2	1.5	0	—
Tertiary lues	2.0	34	0	+
Typhoid fever	3.8	3	0	—

CONCLUSIONS

1. The potassium content of uncentrifuged cerebrospinal fluid is higher than that of the centrifuged fluid.

2. No relation was found between the number of cells in the fluid and its potassium content.

3. No relation was found between the potassium content and the globulin reaction.

4. We do not think that it is possible on the basis of the potassium content to draw any conclusions as regards the character of the condition present in the cerebrospinal system.

5. The potassium content of the cerebrospinal fluid in thirty-one cases is presented. One of these cases with a very high potassium

content (18.3 mg.) was extremely acute, and this one case seems to bear out Salkowski's assertion that the potassium content is high in the acute cases.

6. The potassium content of the cerebrospinal fluid is not increased in degenerative diseases of the cerebrospinal system.

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THE RELATION BETWEEN THE PHENOLSULPHONEPHTHALEIN EXCRETION IN THE URINE AND THE NON-PROTEIN NITROGEN CONTENT OF THE BLOOD IN HUMAN CASES*

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Last year one of us[1] in conjunction with Drs. Fitz, Folin and Denis compared the phenolsulphonephthalein excretion test in the urine with the non-protein nitrogen content of the blood in rabbits, in which an acute nephritis had been produced by the injection of uranium nitrate. It was found in this study that, although these two tests for renal function in a general way responded similarly in acute experimental nephritis in rabbits, there were certain variations. The excretion of the dye in the urine seemed to be a very fair indication of the rabbit's renal ability at the time of injection. On the other hand, the amount of retained non-protein nitrogen in the blood could be used as an indication of the renal efficiency at the moment only, provided the previous condition of the kidney was considered. No conclusions were drawn with regard to the prognostic value of these two tests in this study.

It was decided to continue during the past winter the comparative study of these two tests for renal function in a variety of human cases, especially those in which nephritis existed. It must be remembered that in the human cases more than one organic lesion is frequently present which may complicate the interpretation of the results from these two tests. It was hoped that the relative prognostic value of these tests would also be brought out by this study. In addition the systolic and diastolic blood-pressure and the pulse-pressure were studied in order to see if there was any relation between the height of the blood or pulse-pressure and the other tests.

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* Submitted for publication, June 1, 1914.

* From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard University.

1. Frothingham, C., Fitz, R., Folin, Otto, and Denis, W.: The Relation Between Non-Protein Nitrogen Retention and Phenolsulphonephthalein Excretion in Experimental Uranium Nephritis, THE ARCHIVES INT. MED., 1913, xii, 245.

With regard to these two and other tests for renal function much has been written. It is not our intention to attempt to review the literature on the subject. Fitz[2] has taken up the subject of tests for renal function in a recent communication in which he gives about forty references to recent articles. From these the earlier works on the subject may readily be found.

It must be borne in mind that no single test as yet devised indicates the entire renal function. The phenolsulphonephthalein excretion test and the non-protein nitrogen content of the blood are in favor, at present, because they seem to indicate the renal function as a whole better than any other single test. The latter test has been rendered practical by the simple and accurate method for determination of the non-protein nitrogen in the blood introduced by Folin and Denis.[3] Recently Agnew[4] has reported on a comparative study of these two tests. He concludes that when the excretion of phenolsulphonephthalein is below 40 per cent. there is a definite increase in the incoagulable nitrogen of the blood except in a case of pyelonephritis and in cases with broken cardiac compensation. He places his standard for normal non-protein nitrogen in the blood at 40 to 50 mg. per hundred c.c., which is higher than that set by Folin and Denis.[5] Our study makes us feel that the standard for the non-protein nitrogen content set by Folin and Denis at between 20 and 30 mg. per hundred c.c. of blood is the proper one for the normal. Folin, Denis and Seymour[6] have also compared these two tests and the blood-pressure. They find little if any relation between the height of the blood-pressure and the nitrogen retention.

The cases reported below were practically all in the wards of the Peter Bent Brigham Hospital. The phenolsulphonephthalein tests were made by one of us or by the house officers. Sufficient comparisons were made to see that the house-officer's readings and ours were practically the same. For this test 6 mg. of phenolsulphonephthalein were injected intramuscularly as originally described by Rowntree and Geraghty.[7] The urine was collected at the end of one hour and again

2. Fitz: Amer. Jour. Med. Sc., in press, 1914.
3. Folin and Denis: Jour. Biol. Chem., 1912, xi, 493.
4. Agnew, J. H.: Comparative Study of Phenolsulphonephthalein Elimination and the Incoagulable Nitrogen of the Blood in Cardiorenal Diseases, THE ARCHIVES INT. MED., 1914, xiii, 485.
5. Folin and Denis: Jour. Biol. Chem., 1913, xiv, 29.
6. Folin, D., Denis, W., and Seymour, M.: The Non-Protein Nitrogenous Constituents of the Blood in Chronic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism, THE ARCHIVES INT. MED., 1914, xiii, 224.
7. Rowntree and Geraghty: Jour. Pharmacol. and Exper. Therap., 1910, i, 579.

at the end of the second hour. The readings were made independently on the two specimens, and the sum of the two recorded. Nothing of importance could be noted in recording separately the results for each hour. The phenolsulphonephthalein test was as a rule made on the same day, occasionally on the next day to that on which the blood was collected for the determination of the non-protein nitrogen.

For the estimation of the non-protein nitrogen, blood was taken from the vein and mixed with potassium oxalate crystals to prevent clotting. Five c.c. of this blood were mixed with acetone-free methyl alcohol up to 50 c.c. and allowed to stand for at least two hours. The non-protein nitrogen was then estimated by the method as originally described by Folin and Denis. In most of the cases the nitrogen determinations were made independently by both of us. Usually the results agreed within a few milligrams. The higher reading is recorded in the table, as experience taught us that it was easier to lose some of the nitrogen in the test than to overestimate it. In a few cases in which the results did not agree within reasonable limits the observation was not recorded.

In this work 140 observations were made on 77 individuals. Most of the cases were diagnosed as chronic nephritis with or without other organic lesions. Several cases, however, in which there was no apparent renal disease were included.

The results are recorded in the accompanying table. In the column designated "disease" are recorded the more important diagnoses made at the hospital, and a statement with regard to the presence of edema and cardiac compensation at the time of the test.

It will be readily seen from this table that there are many cases diagnosed clinically and by laboratory tests as those of chronic nephritis, which show a normal phenolsulphonephthalein elimination and a normal non-protein nitrogen content in the blood.

In order to bring out the relation between the two tests and the blood-pressure more clearly the accompanying chart has been prepared. The nitrogen determinations have been divided into groups according to the amount per hundred c.c. of blood thus:

Group	1	includes	13	non-protein nitrogen determinations	between	10- 20
Group	2	includes	52	non-protein nitrogen determinations	between	20- 30
Group	3	includes	32	non-protein nitrogen determinations	between	30- 40
Group	4	includes	12	non-protein nitrogen determinations	between	40- 50
Group	5	includes	3	non-protein nitrogen determinations	between	50- 60
Group	6	includes	2	non-protein nitrogen determinations	between	60- 70
Group	7	includes	7	non-protein nitrogen determinations	between	70- 80
Group	8	includes	3	non-protein nitrogen determinations	between	80- 90
Group	9	includes	4	non-protein nitrogen determinations	between	90-100
Group	10	includes	4	non-protein nitrogen determinations	between	100-200
Group	11	includes	6	non-protein nitrogen determinations	between	200-300
Group	12	includes	2	non-protein nitrogen determinations	between	300-400

RECORDS OF NON-PROTEIN NITROGEN IN BLOOD AND PHENOLPHTHALEIN EXCRETION

GROUP 1

Hosp. No.	Blood Nitrogen mg. per 100 c.c.	Phthalein Total 2 Hrs.	Blood-Pressure	Disease
396	13.0	57	115- 75	Diabetes mellitus.
454	14.7	78	115- 64	Diabetes mellitus.
577	16.1	47	140- 90	Chronic nephritis, no edema.
536	16.6	50	110- 65	Pulmonary and peritoneal T. B., edema.
591	17.4	43	130- 90	Myxedema, no edema.
728	18.5	56	130- 90	Diabetes, myocarditis, no edema.
604	19.3	72	130- 90	Chlorosis, no edema.
913	19.4	60	105- 70	Diabetes insipidus, no edema.
680	19.5	41	190-100	Chronic nephritis, diabetes, edema.
650	19.5	75	170-100	Chronic nephritis, hypertension, slight edema.
818	19.5	59	130- 90	Pleurisy serofibrinous, no edema.
603	19.6	75	194-112	Hyperthyroidism, no edema.
836	19.6	38	230-130	Chronic nephritis, hypertension, no edema.

GROUP 2

513	20.7	40	120- 85	Chronic cardiac valvular and fibrillation, broken compensation, edema.
589	20.8	37	198-115	Chronic nephritis, chronic myocarditis, arteriosclerosis, edema and broken compensation.
590	20.8	29	135- 90	Chronic nephritis, chronic cardiac, no edema, compensation.
680	20.9	30	190- 90	Chronic nephritis, diabetes.
939	20.9	25	115- 80	Chronic cardiac, myxedema, broken compensation.
624	21.1	55	210-130	Chronic nephritis, arteriosclerosis, hypertension, no edema, compensation.
684	21.2	47	220-130	Chronic nephritis, hypertension, compensation, no edema.
428	21.5	51	122- 80	Chronic nephritis, slight edema.
675	21.6	55	150- 90	Chronic nephritis, no edema, compensation.
631	21.7	37	175-110	Chronic nephritis, chronic cardiac, slight edema, broken compensation.
942	21.8	48	170- 85	Diabetes mellitus.
G	21.9	50	.....	Chronic nephritis, no edema, compensation.
739	22.8	58	235- 95	Chronic nephritis, hypertension, compensation, no edema.
672	23.0	42	200-120	Chronic nephritis, arteriosclerosis, no edema.
828	23.1	61	130- 85	Chronic cardiac, broken compensation, no edema.
897	23.2	59	200- 95	Pelvic cancer, no edema, compensation.
548	23.2	35	210- 80	Chronic nephritis and endocarditis, no edema.
460	23.3	50	180-120	Specific aortitis, chronic myocarditis, no edema.
684	23.3	70	210-110	Chronic nephritis, hypertension, compensation, no edema.
1030	23.4	75	230-170	Cirrhosis liver, hypertension, compensation, no edema.
684	23.8	69	220-110	Chronic nephritis, hypertension, no edema, compensation.
1075	23.8	55	192-110	Chronic nephritis, edema, compensation.
428	23.9	45	145-100	Chronic nephritis, no edema.

RECORDS OF NON-PROTEIN NITROGEN IN BLOOD—(Continued)

GROUP 2.—(Continued)

Hosp. No.	Blood Nitrogen mg. per 100 c.c.	Phthalein Total 2 Hrs.	Blood-Pressure	Disease
513	24.2	40	120- 70	Chronic cardiac, valvular, fibrillating, slight edema, broken compensation.
1046	24.7	40	170-110	Chronic nephritis, hypertension, no edema, compensation.
428	24.7	52	.....	Chronic nephritis, slight edema.
620	24.9	20	180-104	Chronic valvular disease, edema.
986	25.3	50	190-125	Chronic nephritis, hypertension, moderate edema, fair compensation.
624	25.4	45	225-124	Arteriosclerosis, hypertension, no edema, fair compensation.
722	25.5	46	210-150	Arteriosclerosis cerebral, no edema.
739	25.5	52	215- 80	Chronic nephritis, hypertension, compensation, no edema.
571	25.6	60	220-150	Chronic nephritis, syphilis, no edema.
816	25.9	51	190-110	Chronic nephritis, cirrhosis of liver with edema, hypertension.
657	26.1	65	145-100	Chronic nephritis, no edema, tonsillitis.
316	26.1	67	135- 95	Chronic nephritis, cirrhosis, arteriosclerosis.
963	26.1	43	165- 95	Chronic arthritis, no edema, compensation.
1023	26.3	40	215-150	Chronic nephritis, hypertension, slight edema, compensation.
684	27.0	58	185-110	Chronic nephritis, hypertension, no edema, compensation.
920	27.0	58	120- 50	Chronic cardiac, no edema, compensation.
684	27.7	57	210-120	Chronic nephritis, hypertension, no edema, compensation.
876	27.7	50	130- 70	Chronic cardiac, broken compensation.
991	28.0	70	130- 80	Diabetes, no edema, compensation.
782	28.4	66	160- 85	Chronic nephritis, rheumatism, hypertension, compensation, no edema.
1029	28.5	66	185- 70	Chronic nephritis, hypertension, no edema, compensation.
624	28.5	50	210-130	Chronic nephritis, arteriosclerosis, compensation, no edema.
928	28.8	30	170-100	Chronic nephritis, myocarditis, hypertension, no edema.
589	29.0	50	195-110	Chronic nephritis, myocarditis, arteriosclerosis, slight edema, fair compensation.
675	29.0	43	150- 90	Chronic nephritis, no edema, compensation.
590	29.2	33	145-110	Chronic nephritis, chronic cardiac, no edema, fair compensation.
672	29.4	48	180-120	Chronic nephritis, arteriosclerosis, no edema.
609	29.8	41	218-120	Chronic nephritis, hypertension, arteriosclerosis, no edema, compensation.
672	29.9	43	220-140	Chronic nephritis, arteriosclerosis, no edema.
			GROUP 3	
817	30.0	53	220-130	Chronic nephritis, hypertension, no edema, compensation.
836	30.3	46	210-120	Chronic nephritis, hypertension, no edema.
701	31.0	45	160-100	Chronic nephritis, chronic myocarditis, no edema, fair compensation.
837	31.0	49	115- 72	Chronic cardiac, broken compensation, no edema.

RECORDS OF NON-PROTEIN NITROGEN IN BLOOD—(Continued)

GROUP 3.—(Continued)

Hosp No.	Blood Nitrogen mg. per 100 c.c.	Phthalein Total 2 Hrs.	Blood-Pressure	Disease
856	31.2	26	100- 80	Chronic nephritis, chronic myocarditis, edema, broken compensation.
876	31.2	30	240-160	Chronic nephritis, hypertension, no edema, compensation.
624	31.2	50	210-120	Chronic nephritis, arteriosclerosis, compensation, no edema.
719	31.4	28	128- 80	Chronic cardiac, fair compensation.
1045	31.6	50	220-120	Chronic nephritis, hypertension, no edema compensation.
817	31.8	63	220-145	Chronic nephritis, hypertension, no edema, compensation.
678	31.9	30	165-130	Chronic nephritis, no edema, compensation, hypertension.
609	32.8	47	225-128	Chronic nephritis, hypertension, arteriosclerosis, no edema, compensation.
782	33.3	52	175-115	Chronic nephritis, rheumatism, hypertension, compensation, no edema.
763	33.3	52	200-120	Chronic nephritis, arteriosclerosis, hypertension, slight edema, fair compensation.
791	33.4	75	210-150	Chronic nephritis, arteriosclerosis, chronic myocarditis, hypertension, no edema, compensation.
873	33.5	31	160- 65	Chronic nephritis, no edema, compensation.
675	34.0	54	170-105	Chronic nephritis, slight edema, compensation.
873	34.2	62	135- 60	Chronic nephritis, no edema, compensation.
631	34.7	49	190-120	Chronic nephritis, chronic cardiac, no edema, fair compensation.
854	34.9	42	130- 90	Gastroptosis, temporary hypertension.
817	35.2	51	195-130	Chronic nephritis, hypertension, no edema, compensation.
678	35.4	33	164-	Chronic nephritis, no edema, compensation, hypertension.
918	35.4	40	.....	Chronic nephritis, compensation, no edema.
848	35.7	48	145- 90	Chronic cardiac, acute rheumatism, broken compensation, no edema.
684	35.9	65	210-110	Chronic nephritis, hypertension, no edema, compensation.
739	36.5	32	230-110	Chronic nephritis, hypertension, compensation, no edema.
343	37.1	43	.....	Chronic cardiac, arteriosclerosis.
739	37.5	35	200- 90	Chronic nephritis, hypertension, compensation, no edema.
763	39.0	46	205-130	Chronic nephritis, arteriosclerosis, hypertension, no edema, fair compensation.
763	39.0	48	200-120	Chronic nephritis, arteriosclerosis, hypertension, edema.
428	39.1	45	140- 90	Chronic nephritis, edema free.
762	39.8	18	175-125	Chronic nephritis, hypertension, no edema, compensation.

GROUP 4

589	43.4	22	170-100	Chronic nephritis, chronic myocarditis, arteriosclerosis, no edema, fair compensation.
762	43.4	35	195-125	Chronic nephritis, hypertension, edema, broken compensation.

RECORDS OF NON-PROTEIN NITROGEN IN BLOOD—(Continued)

GROUP 4.—(Continued)

Hosp. No.	Blood Nitrogen mg. per 100 c.c.	Phthalein Total 2 Hrs.	Blood-Pressure	Disease
762	44.7	16	180-130	Chronic nephritis, hypertension, no edema, fair compensation.
631	45.7	25	210-142	Chronic nephritis, chronic cardiac, broken compensation, edema.
627	46.9	17	155- 90	Chronic nephritis, arteriosclerosis, edema, broken compensation.
678	46.9	42	160-110	Chronic nephritis, no edema, compensation, hypertension.
762	47.6	25	190-120	Chronic nephritis, hypertension, slight edema, fair compensation.
1127	47.8	35	238-135	Chronic nephritis, diabetes, hypertension, pending uremia, compensation.
631	47.8	37	175-135	Chronic nephritis, chronic cardiac broken compensation, edema.
974	48.1	25	190-120	Chronic nephritis, hypertension, no edema, compensation.
675	49.0	37+	140- 85	Chronic nephritis, no edema, compensation.
739	49.0	23	220- 90	Chronic nephritis, hypertension, compensation, no edema.
			GROUP 5	
762	50.0	36	175-110	Chronic nephritis, hypertension, slight edema, fair compensation.
974	54.1	25	180-120	Chronic nephritis, hypertension, no edema, compensation.
762	56.1	18	195-130	Chronic nephritis, hypertension, no edema, fair compensation.
			GROUP 6	
627	62.8	34	140- 90	Chronic nephritis, chronic cardiac, slight edema, broken compensation.
950	69.9	48	140- 90	Chronic nephritis, chronic cardiac, slight edema, broken compensation.
			GROUP 7	
918	70.9	14	240-170	Chronic nephritis, hypertension, edema, broken compensation.
950	73.0	27	140- 90	Chronic nephritis, chronic cardiac, edema, broken compensation.
918	75.7	25	260-190	Chronic nephritis, hypertension, no edema, fair compensation.
762	76.8	15	170-120	Chronic nephritis, hypertension, no edema, compensation.
762	78.7	12	150-110	Chronic nephritis, hypertension, no edema, compensation.
1056	78.8	Trace	210-115	Chronic nephritis, hypertension, pending uremia, slight edema, fair compensation.
918	79.6	20	268-198	Chronic nephritis, hypertension, slight edema, fair compensation.

RECORDS OF NON-PROTEIN NITROGEN IN BLOOD—(Continued)

GROUP 8

Hosp. No.	Blood Nitrogen mg. per 100 c.c.	Phthalein Total 2 Hrs.	Blood-Pressure	Disease
1056	87.0	Trace	210-105	Chronic nephritis, pending uremia, hypertension, compensation, no edema.
762	88.0	33	140-100	Chronic nephritis, hypertension, no edema, compensation.
655	89.2	3	220-145	Chronic nephritis, no edema, pending uremia.

GROUP 9

621	90.0	3	280+-160	Chronic nephritis, pending uremia, hypertension, no edema, compensation.
573	90.4	3	240-130	Chronic nephritis, no edema.
655	96.1	28	230-144	Chronic nephritis, no edema, pending uremia.
655	96.1	Trace	230-144	Chronic nephritis, no edema, pending uremia.

GROUP 10

895	117.0	0	194-120	Chronic nephritis, uremia, no edema, compensation.
573	117.0	2	230-130	Chronic nephritis, no edema, pending uremia.
655	129.8	0	220-170	Chronic nephritis, no edema, pending uremia.
1056	129.8	Trace	210-100	Chronic nephritis, uremia, hypertension, no edema, compensation.

GROUP 11

573	200.0	0	215-130	Chronic nephritis, uremia, no edema.
673	209.0	0	195-124	Chronic nephritis, hypertension, no edema.
1058	212.0	Trace	.....	Chronic nephritis, uremia, edema, broken compensation.
655	278.0	0	230-165	Chronic nephritis, uremia, no edema.
673	285.7	0	205-130	Chronic nephritis, hypertension, uremia, no edema.
673	288.0	0	195-110	Chronic nephritis, hypertension, pending uremia, no edema.

GROUP 12

655	330.0	Anuric	180-120	Chronic nephritis, uremia, no edema.
655	347.0	Anuric	180-110	Chronic nephritis, uremia, no edema.

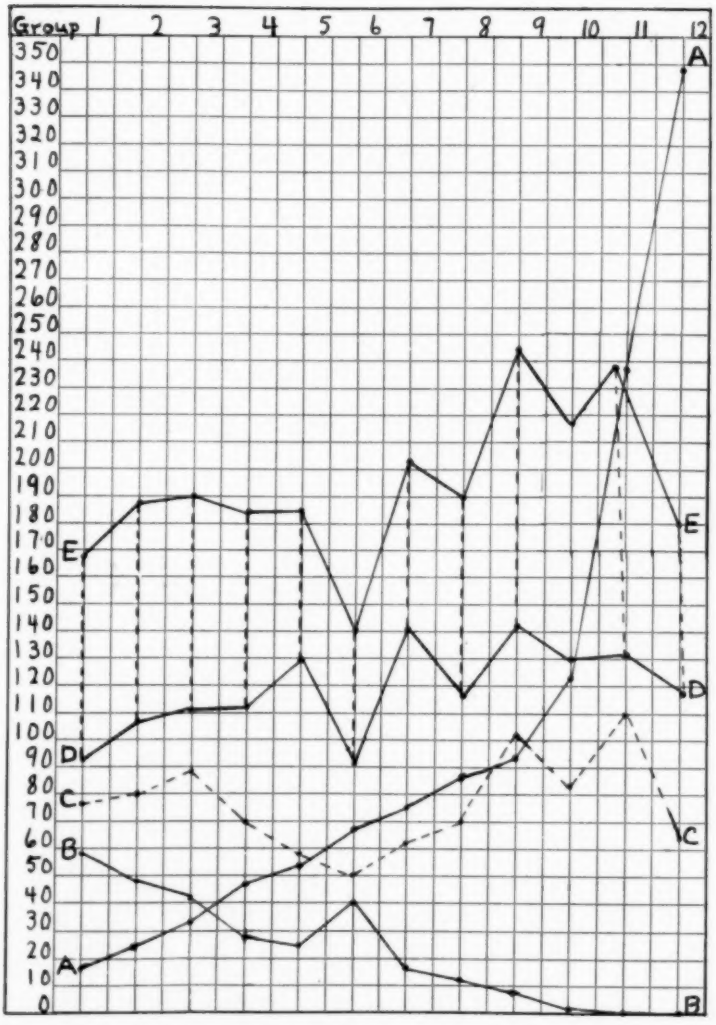

Chart showing as follows: .—A-A, Non-protein nitrogen in the blood; B-B, phenolsulphonephthalein excretion; C-C, pulse-pressure; D-D, diastolic blood-pressure; E-E, systolic blood-pressure.

The average of the non-protein nitrogen determinations in each group has been taken and also the average of the phenolsulphonephthalein excretion for these same cases. In averaging the blood-pressures it seems fairer to leave out the cases in which chronic nephritis was not present because the blood-pressure in these cases was considerably lower. The non-nephritic cases did not affect the non-protein nitrogen or phenolsulphonephthalein averages, for they occurred only in those groups in which the non-protein nitrogen and phenolsulphonephthalein fell within normal limits.

From the accompanying chart it is readily seen that the phenolsulphonephthalein excretion steadily falls as the amount of non-protein nitrogen in the blood increases, except in Group 6, which is composed of only two cases. When the non-protein nitrogen reaches the hundred mark the elimination of the dye within the two hours practically ceases. Marked increase in non-protein nitrogen in the blood of over 150 mg. per hundred c.c. appeared from our cases to come on just a few days preceding death, and we looked on it as a terminal phase of the disease. The relation between the blood-pressure and the pulse-pressure and the other tests is not so definite. The systolic pressure averaged slightly higher in the groups with the nitrogen above 70 mg. (except in Group 12) than in Groups from 1 to 6. The pulse-pressure, however, showed no definite relation to the other tests.

If, on the other hand, the observations are considered individually, it is found that considerable variation occurs between the phenolsulphonephthalein excretion in different cases in the same group in which of course the non-protein nitrogen content varies but little. The same may also be said of the blood-pressure. Thus, for example, in Group 1, the phenolsulphonephthalein excretion varies from 38 per cent. to 78 per cent., in Group 2 from 20 per cent. to 75 per cent., in Group 3 from 18 per cent. to 75 per cent. In the other groups, except 10, 11 and 12, variations occur of anywhere from 15 per cent. to 35 per cent. in a group.

In order to discover if there was any complicating factor which might influence the excretion of the phenolsulphonephthalein, the clinical records were carefully studied in those cases in which the individual phthalein excretion was 10 per cent. below or above the average of its group. No pathological condition was found constantly present to account for the increase in phenolsulphonephthalein excretion. Several reports have appeared in the literature from time to time in which the phenolsulphonephthalein excretion has been unexpectedly high without any satisfactory explanation being given, and we feel that our work has not thrown any light on that point.

In a considerable number of the cases in which the phenolsulphonephthalein excretion was below the average either edema or broken compensation was shown to some degree. We therefore agree with the view already expressed by others that the excretion of the phenolsulphonephthalein is influenced by passive congestion but that the non-protein nitrogen content in the blood is not. On the other hand, patients with broken cardiac compensation frequently excreted a normal amount of phthalein. In a moderate number of cases, however, a surprisingly low phenolsulphonephthalein excretion was shown for which no cause could be found either from the clinical findings or laboratory tests. It seems fair, therefore, to say that a considerable individual variation above or below the expected average may occur in the phenolsulphonephthalein test for which no cause can be found. The relation between the non-protein nitrogen content of the blood and the clinical findings is fairly uniform. No non-nephritic cases showed an increase of non-protein nitrogen in the blood. All the patients with the non-protein nitrogen content above 50 mg. per hundred c.c. of blood either died or left the hospital with evidence, clinically and from other laboratory tests, of a severe nephritis. In some of these cases the phenolsulphonephthalein excretion was at times fairly good. The cases with a non-protein nitrogen content above 35 mg. per hundred c.c. of blood, except when it was forced up by special diet, usually appeared clinically to be a more severe grade of nephritis than the cases without such a high non-protein nitrogen content.

CONCLUSIONS

Many cases of chronic nephritis show normal phenolsulphonephthalein excretion and normal non-protein nitrogen content in the blood.

The content of non-protein nitrogen in the blood varies in a rough way inversely with the excretion of phenolsulphonephthalein in the urine in nephritis. The phenolsulphonephthalein excretion is influenced by cardiac decompensation and other unknown factors so that quite unexpected results occur in individual cases.

The content of non-protein nitrogen in the blood seems to be less influenced by cardiac and other complicating factors.

The amount of non-protein nitrogen in the blood seems to be of considerable prognostic value.

The height of the blood-pressure and the pulse-pressure do not seem to be of prognostic importance in nephritis.

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A POINT TO BE CONSIDERED IN THE USE OF THE ABDERHALDEN REACTION *

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Abderhalden has demonstrated that the parenteral introduction into the body of foreign protein or other material results in the appearance in the blood-serum of ferments capable of splitting these foreign substances into bodies which are less disharmonious with the organism. He has shown that these ferments are produced only by the presence in the blood of the corresponding material and that they seem to be specific; that is to say, that they are capable of splitting only the one particular variety of protein, or other substance, the injection of which resulted in their formation.

The dialysis method, by which proteolytic ferments may be detected, recommended by Abderhalden, consists essentially of two parts. First, about 0.5 gm. of sterile protein (which must be free from substances which react with ninhydrin) is placed with 1.0 to 1.5 c.c. of the sterile blood-serum under test, free from hemoglobin and blood-cells, in a sterile, tested, and standardized dialyzing thimble. This is then floated in 20 c.c. of sterile water in a sterile vessel and the whole incubated at blood temperature for sixteen hours. Secondly, 10 c.c. of the dialysate is boiled for exactly one minute with 0.2 c.c. of a 1 per cent. solution of ninhydrin. The appearance or non-appearance of a blue color within half an hour is an indication of the presence or absence of amino-acids, polypeptids or peptones (and other substances) and from this it is deduced that lysis of the protein material used in the test has or has not occurred, and hence that the blood-serum does or does not contain a proteolytic ferment for this particular protein. Control tests with the various substances used are obviously necessary.

The discovery of these facts has led to the suggestion that in this reaction we have a means of detecting destruction by injury or disease of any organ within the body; for it is claimed that some of the proteins of which each organ is composed are peculiar to that organ and under conditions of ordinary healthy life do not enter the blood-stream. Destruction of an organ within the body, however produced, leads to the absorption of the specific protein peculiar to it, and although some splitting and lysis probably occurs within the bodies of the migratory

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* From the Laboratory of the Illinois State Psychopathic Institute.

cells which must act as the medium for the transfer of this dead protein to the blood-stream, yet it may be that the substance which finally gains admission to the circulation still retains the essential specific molecular construction of the original tissue protein. This would then give rise to the production of proteolytic ferments in the blood-serum specific for the proteins peculiar to the organ which has been destroyed.

This suggestion has been seized by many workers with the greatest enthusiasm and within the two years which have elapsed since the publication of Abderhalden's work an enormous literature has been built up dealing with investigations into pathological conditions of all kinds. Especially true is this in regard to the disorders grouped under the head of psychiatry.

A study of this literature reveals the most contradictory and confusing results, a state of affairs which seems inevitable when the complexity of the series of chemical changes already indicated in the passage of the dead protein from the organ to the blood-stream is considered. When to this is added the rigid and exacting nature of the technic of the final test, the sources of possible error become enormous. To illustrate the situation, reference may be made to the findings in dementia praecox. Fauser claims to have demonstrated that the serum of these patients always contains ferments which will digest the proteins of sex glands and that other types of mental disorder do not show this phenomenon. He is supported by the observations of many others. Yet even among those who more or less conform to this view we find that Kafka,[1] for instance, reports the digestion of ovary by male serum and of testis by female serum, although he makes no comments on these results. Other observers, on the other hand, not only fail to find such digestion in all cases of dementia praecox, but do find it in other psychoses. Reference may be made, for instance, to the careful work of Simon,[2] who reports that in 12 per cent. of the cases of dementia praecox examined by him, the serum contained no proteolytic ferment for sex gland, while in 30 per cent. of the other forms of psychosis investigated the serum did possess this property.

So far has enthusiasm been carried that it is quite common to find authors suggest that all observations, whether by themselves or others, which do not conform to the views with which they start are the result of faulty technic, while others even suggest that the clinical diagnosis was incorrect. Even does one find commercial laboratories which make returns "positive or negative for dementia praecox."

1. Kafka: Ztschr. f. d. ges. Neurol. u. Psychiat., 1913, xviii, 348, Cases 11 and 31.

2. Simon, Charles E.: The Abderhalden-Fauser Reaction in Mental Diseases with Special Reference to Dementia Praecox, Jour. Am. Med. Assn., 1914, lxii, 1701.

In view of the far-reaching conclusions which are being so confidently drawn and of the contradictory results which have been obtained, it seems that more methodical and careful study of the fundamental problems concerned is eminently desirable.

In the first place, it is difficult to understand why, if tissues like placenta and carcinoma give rise to the appearance in the blood-serum of protective enzymes, the normal tissue cells of the body should not do so likewise. That Abderhalden seems to admit that cell metabolism may have this effect is apparent from his statement in a recent paper[3] read before the American Medical Association, that "one must abandon the frequently accepted view that the appearance of protective enzymes or of new blood enzymes in general is associated with cell destruction." With this question in view it was decided to make a series of tests on the tissues and serums of healthy dogs and cats. This has led to certain findings which appear of considerable importance.

EXPERIMENTAL WORK

The animal was anesthetized with ether. The two jugular veins were dissected out and sterile cannulas were inserted into each end of the cut veins of either side. Blood for serum was drawn into sterile tubes, from a vein or sometimes from the carotid artery. The proximal ends of the veins were connected with a tank containing 0.9 per cent. salt solution. As soon as sufficient blood for serum had been collected, the blood was allowed to flow from the distal ends of the veins. At the same time the salt solution was allowed to enter the blood-stream. This arrangement was allowed to remain till the outcoming fluid was colorless or very slightly pink. Sometimes just before the death of the animal, ammonium oxalate was added to the salt solution. This solution was allowed to run into the body for about ten minutes and then the connections were made with a tank of distilled water so that this water was infused into the body instead of the salt solution.

After the infusion was over the organs were very free from blood. The body was opened and the following organs were removed: brain, thyroid, liver, spleen, pancreas, kidneys, suprarenals and sex glands.

Each of these organs was separately minced and boiled for ten or fifteen minutes with water containing about five drops of acetic acid per liter. The mixture was then filtered. The washing was repeated five to seven times. The tissues were then put into test-tubes which

3. The Present Status of the Investigation of the Protective Enzymes, read before the Section on Obstetrics at the sixty-fifth annual session of the American Medical Association, Atlantic City, N. J., June, 1914. This has not yet been published, but a copy was kindly furnished by Prof. A. J. Carlson of the University of Chicago.

were stoppered with cotton plugs. These were then sterilized for half an hour in steam at 5 pounds' pressure.

Blood was also prepared as a substrate. It was washed, boiled and sterilized in exactly the same manner as the tissues.

The blood collected for serum was allowed to stand till the serum separated well from the clot. The serum was removed by decantation or centrifugation and then again centrifuged.

When blood was collected for serum without killing the animal, it was taken with a sterile needle from the saphenous vein.

The parts for the test were assembled as follows: Twenty c.c. of sterile distilled water was placed with a sterile pipet into each cotton-plugged sterile test-tube (1 inch in diameter and 8 or 10 inches long). The sterile dialyzing thimble was lifted with sterile forceps and held while the sterile substrate and serum, either or both, were introduced. The dialyzing tube was then let gently into the water in the test-tube and the latter again closed. A single complete test consisted of one test with serum alone in the dialyzing-tube, one test with substrate alone and one test with serum and substrate together. The combinations were incubated at 37 C. for sixteen hours. After the incubation, 10 c.c. of the dialysate was measured out into a clean large test-tube. To this was added 0.2 c.c. of a 1 per cent. solution of ninhydrin. This solution was boiled strongly for exactly one minute. The color was noted and recorded as negative, questionable, positive, double positive or triple positive, meaning respectively, no color, suspicion of color, just enough blue to be easily seen, an amount of blue about midway between the latter test and the next, and finally, so much blue that it was difficult to see through it against a white background. The result of the complete test was considered positive if the color of the dialysate from the tissue and serum was more intense than the combined color of the other two dialysates. It was considered questionable when the intensity of the color of this dialysate was equal to the other two. The test was negative either when there was no blue color in the tested dialysate of the tissue and serum or when the color was markedly less than the intensity of that of the other two combined. The dialysing thimbles had been tested first for permeability to albumin. They should not allow protein to pass through them. Egg-white was used as substrate and the biuret test for albumin employed in place of the ninhydrin.

The dialysing tubes were next tested for permeability to peptone and standardized in this respect. The regular test was carried out, except that 1 c.c. of 10 per cent. solution of peptone was used in place of the substrate and serum. Those tubes giving a test with ninhydrin of less than a double positive were discarded. Those tubes allowing peptone to pass through sufficiently to give a double positive result with

TABLE 1.—Results with a Strict Abderhalden Technic*

Tissue	No. of Tests	Immediately After Boiling for One Minute		After Standing for Half an Hour	
		Positive	Doubtful	Positive	Doubtful
Blood (1)	21	9	1	12	2
Brain (2)	20	4	1	8	3
Kidney	22	7	1	9	2
Liver (3)	32	5	0	7	2
Pancreas (4)	11	1	0	1	2
Spleen (5)	15	9	1	7	4
Suprarenal	5	1	0	2	0
Sex glands	6	3	0	3	1
Thyroid (6)	9	3	0	4	0

*Included with the foregoing figures are the results of tests in which incubation was prolonged to twenty-four hours. The number of tests and the results with this variation were:

Tissue	No. of Tests	Immediately After Boiling	After Standing One-Half Hour
1	2	Positive	Positive
2	1	Negative	Doubtful
3	2	Negative	Negative
4	2	Negative	Doubtful
5	1	Negative	Negative
6	2	Positive	Positive

TABLE 2.—Results with Strict Abderhalden Technic Expressed in Percentages

Tissue	Immediately After Boiling for One Minute		After Standing for Half an Hour	
	Positive	Negative	Positive	Negative
Blood	43	52	57	33
Brain	20	75	40	45
Kidney	32	65	41	50
Liver	16	84	22	72
Pancreas	9	91	9	73
Spleen	60	33	47	27
Supararenal ..	20	80	40	60
Sex Gland....	50	50	50	33
Thyroid.....	33	67	44	56
Average ...	32	66	38	50

ninhydrin were marked and those giving a triple positive test were also marked. These two classes of tubes were kept separate and no complete test was made in which tubes of the two classes were used together.

The results of 141 tests with a strict Abderhalden technic are given in Tables 1 and 2.

TABLE 3.—Results with Incubation for Twenty-Four Hours and Substitution of 0.9 Per Cent. Salt Solution for Distilled Water in the Dialyser

Tissue	No. of Tests	Immediately After Boiling for One Minute		After Standing for Half an Hour	
		Positive	Doubtful	Positive	Doubtful
Blood	10	2	0	3	2
Brain	10	6	0	2	2
Kidney	9	5	0	4	1
Liver	12	5	0	4	2
Pancreas	5	2	0	1	1
Spleen	11	5	0	4	0
Suprarenal	4	2	1	2	1
Sex gland	5	4	0	2	2
Thyroid	6	3	0	2	2

TABLE 4.—Results in Table 3 Expressed in Percentages

Tissue	Immediately After Boiling for One Minute		After Standing for Half an Hour	
	Positive	Negative	Positive	Negative
Blood	20	80	30	50
Brain	60	40	20	60
Kidney	56	44	44	44
Liver	42	58	33	50
Pancreas	40	60	20	60
Spleen	45	55	36	64
Suprarenal ...	50	25	50	25
Sex gland ...	80	20	40	20
Thyroid	50	50	33	33
Average	49	48	34	45

The results given in Tables 1 and 2 prove quite conclusively that the serum of normal animals may frequently contain ferments capable of splitting the protein in a number of the tissues of the body. Similar results were obtained by Lichtenstein and Hage.[4]

4. Lichtenstein, S., and Hage: Nachweis von spez. Fermenten mit Hilfe des Dialysierverfahrens, München. med. Wchnschr., 1914, lxi, 915.

If the animals we used were all normal healthy animals, as they all seemed to be, there should have been a more uniform set of results. It seems that the results on any organ tissue should have been all positive or all negative. It was thought that possibly this variation might have been due to the length of time of incubation and to the character of the medium in which the dialyzing tube was floated. Since it takes time for enzymes to do their work, and it also takes time for substances to dialyze, and also since it takes a certain definite amount of protein decomposition products to give a perceptible ninhydrin reaction, the lengthening of the time of incubation to twenty-four hours might increase the number of positive results. Since the activity of the well-studied ferments of the body is much affected by the medium in which

TABLE 5.—RESULTS IN TABLES 1 AND 3 COMBINED, EXPRESSED IN PERCENTAGES

Tissue	No. Tests	Immediately After Boiling for One Minute			After Standing for Half an Hour		
		Positive	Doubtful	Negative	Positive	Doubtful	Negative
Blood	31	35	4	61	48	13	39
Brain	30	33	4	63	33	17	50
Kidney	31	39	3	58	42	10	48
Liver	44	23	0	77	25	9	66
Pancreas	16	19	0	81	12	19	69
Spleen	26	54	2	44	42	16	42
Suprarenal	9	33	11	56	44	12	44
Sex gland	11	64	0	36	45	28	27
Thyroid	15	40	0	60	40	13	47
Average	213	36	2	62	36	14	50

they act, it was thought important to maintain the original salt concentration of the serum throughout the time of incubation. This would be better accomplished by using a sterile physiological salt solution in place of the distilled water used in the original method. Therefore a number of tests were made modifying the original method in the ways just mentioned; that is, lengthening the time of incubation to twenty-four hours and using 0.9 per cent. salt solution in place of distilled water. The results of seventy-two tests are given in Tables 3 and 4.

Tables 3 and 4 do not show any marked differences in results from those of Tables 1 and 2. The same lack of uniformity exists. As a whole, about the same percentages of positives and negatives occur as when the original method was used.

Since this alteration in the Abderhalden method did not seem to affect the results, we are justified in combining the figures of Tables 1, 2, 3 and 4 in Table 5.

In using the regular method, a number of different serums were used on a series of tissues which were composite mixtures of the same organs of several dogs. Likewise a number of tests were made on the tissues of one dog with the serums of several others. The results are given in Tables 6 and 7.

The uniformity of these results indicates that the irregularity of those previously reported was not due to differences in the serums. On the contrary, it was probably in the substrate, and most likely in its preparation. The preparation of the tissues had been done with the greatest care, and strictly according to the methods prescribed by Abderhalden. In but two cases out of some hundreds of tests made have the substrates alone given a positive ninhydrin reaction.

TABLE 6.—Tests on a Single Set of Composite Tissues with Various Serums

Donor of Serum	Blood	Spleen	Kidney	Liver
Bird-dog	+	—	..	—
Bulldog	+	—	—	—
Dog 5	+	—	—	—
Terrier B. and T.	+	?	—	

TABLE 7.—Tests on Tissues of Dog 5 with Various Serums

Donor of Serum	Blood	Brain	Spleen
Dog 8	—	—	+
Dog 4	—	—	+
Fox terrier ..	—	—	+

In reviewing these facts it occurred to us that there might be some substance or substances in the body tissues which is soluble in boiling water containing 5 drops of acetic acid per liter, capable of being broken down by a serum ferment into parts which would give a blue color with ninhydrin; whereas, before the cleavage, ninhydrin would not give the characteristic reaction. If these suppositions were correct, any or all tissues prepared as a substrate might not or might give a positive reaction according as the substrate were or were not washed free of this material.

An attempt was made to separate this hypothetical substance (or substances). The acid washings from the substrates, prepared in the usual manner, were filtered through the best grade of filter-paper. The filtrate was boiled down to a small volume and an equal volume of absolute alcohol was added. A precipitate was formed in every case. This precipitate was centrifuged out and washed about five times by

centrifugation with equal volumes of water and alcohol. It was then put into a test-tube and set in boiling water for ten or fifteen minutes for the purpose of driving off the alcohol. The tube was then plugged with a cotton stopper and sterilized under steam at about 5 pounds' pressure for twenty minutes. Preparations were made in this manner from brain, kidney, liver, pancreas, spleen, suprarenal, testicle, thyroid and muscle. Emulsions of these preparations were used as substrates in the regular Abderhalden reaction. The results were as shown in Table 8.

TABLE 8.—Tests Made on Preparations from the Acid Washings of Organs in the Process of Preparing These Organs as Substrates

Tissue	Source of Tissue	Donor of Serum	Results		
			Ppte. and Serum	Ppte. Alone	Serum Alone
Brain	Composite	Collie	+	—	—
Brain	Composite	Collie	+	—	—
Kidney	Dog 9	Bulldog	+ + +	—	+
Kidney	Dog 9	Bulldog	+ + +	—	+
Liver	Dog 9	?	+	—	—
Liver	Dog 9	?	+	—	—
Pancreas	Dog 9	Terrier	+ + +	—	+ ?
Spleen	Composite	Sheep-dog	+	—	—
Spleen	Composite	Sheep-dog	+	—	—
Suprarenal	Composite	Collie	+	—	—
Suprarenal	Composite	Collie	+	—	—
Testis	Composite	Sheep-dog	+ +	—	—
Testis	Composite	Sheep-dog	+ +	—	—
Thyroid	Composite	Collie	+ +	—	—
Thyroid	Composite	Collie	+	—	—
Muscle	Bull dog	Collie	+ +	—	—
Muscle	Bull dog	Collie	+ +	—	—

Having found that blood treated like other tissue as a substrate gave some positive results, it seemed admissible to prepare blood free from hemoglobin for a further test. The blood was drawn into a flask containing ammonium oxalate. The corpuscles were centrifuged out and were then broken by being allowed to stand in distilled water over night. The mixture was then centrifuged and the residue washed till free from hemoglobin with distilled water. The solid material was placed in a test-tube plugged with cotton and then sterilized as the other substrates. An emulsion of this substance was made in sterile water and used for the Abderhalden reaction. The results were as follows:

1. Preparation from blood of dog and serum of collie dog ++
2. Preparation from blood of dog and serum of collie dog ++
1. Preparation from blood of dog alone..... —
2. Preparation from blood of dog alone..... —
1. Serum of collie dog alone..... +
2. Serum of collie dog alone..... +

These results show conclusively that there is in each of the tissues with which we worked a substance or a number of substances, which are washed out with acidified water, which do not give a blue color when boiled with ninhydrin, but which are, by normal serum ferments, broken into simpler parts which do give a blue color when boiled with ninhydrin. The question next arose as to whether or not the regular substrates which gave positive results could not have been made negative by further washing and thus freeing the substrate from the materials dealt with above. To demonstrate this point, tests were made on substrates at various stages of washing. The results were as shown in Table 9.

TABLE 9.—Effect of Progressive Washing of Material Used for Substrates

Tissue	No. of Washings	Donor of Serum	Results of Tests		
			Tissue and Serum	Tissue Alone	Serum Alone
Kidney	1	Black	+ + +	+	—
Kidney	1	Terrier	+ + +	—	—
Kidney	1	Collie	+ + +	—	—
Kidney	2	Black	+ +	—	—
Kidney	2	Terrier	+ +	—	—
Kidney	2	Collie	+ +	—	—
Kidney	3	Black	+ +	—	—
Kidney	3	Terrier	+ +	—	—
Kidney	3	Collie	+ ?	—	—
Kidney	5	Black	+	—	—
Kidney	5	Terrier	+ +	—	—
Kidney	5	Collie	+ ?	—	—
Kidney	7	Black	+ +	—	—
Kidney	7	Terrier	+ +	—	—
Kidney	7	Collie	+	—	—
Kidney	12	Sheep-dog	—	—	—
Kidney	12	Black	—	—	—
Kidney	12	Collie	—	—	—
Spleen	5 to 7	Terrier	+ +	—	—
Spleen	5 to 7	Collie	+	—	—
Spleen	5 to 7	Sheep-dog	+	—	—
Spleen	10 to 12	Sheep-dog	—	—	—
Spleen	10 to 12	Collie	—	—	—
Spleen	10 to 12	Black	—	—	—
Muscle	5 to 7	Terrier	+ + +	—	—
Muscle	5 to 7	Collie	+	—	—
Muscle	5 to 7	Sheep-dog	+	—	—
Muscle	10 to 12	Collie	+ +	—	—
Muscle	13 to 15	Collie	+	—	—
Muscle	13 to 15	Black	+	—	—
Muscle	18 to 20	Terrier	—	—	—
Muscle	18 to 20	Sheep-dog	—	—	—
Muscle	18 to 20	Pointer	—	—	—

DISCUSSION AND CONCLUSIONS

It is clear from Tables 1 to 5 that positive Abderhalden tests are frequently obtained with normal serums and substrates prepared from normal blood, brain, kidney, liver, spleen, pancreas, suprarenal, sex gland, thyroid and muscle. From Tables 6 to 9 it is plain that the cause of these positive tests is a material which may be washed out of the substrate, if the washing is continued long enough. Abderhalden's directions for detecting when the substrate is washed enough, however, are not sufficient. The only way to know whether a substrate is fit to use with pathological serums is to have it thoroughly tested with a number of serums from normal persons. If this is not done the results are of small value.

The tests here published show that no definite number of washings can be regarded as sufficient. They must be continued until actual test with normal serums demonstrates the removal of this substance. Abderhalden's directions give no reasons for care in the washing of the substrates, but he does insist[3] on the need for controls of the substrates used for pathological work by testing with normal serums. Unless this be done the results, as Abderhalden states, are entirely worthless. The explanation of the need for this care offered here seems to us to explain many of the discordant results which have been published. We might add that this applies especially to the investigation of reactions with the smaller organs, such as the glands of internal secretion where the amount of material available is small and repeated washing means increased waste.

The published reports of work do not state whether the substrates were always the same in any one series nor how much they were washed, and hence must be studied with caution.

The conclusions may be briefly stated as follows:

1. Using the Abderhalden technic with the Abderhalden reaction, the serums of normal animals frequently show evidence of the presence of ferments capable of digesting various tissues of the body.

2. The material causing the positive Abderhalden reactions between normal serum and normal tissue may be precipitated from the washings by the addition of an equal volume of alcohol.

3. The material causing the positive Abderhalden reactions between normal serum and normal tissue may be completely removed from the substrate if the washing is continued long enough. The number of washings required varies with different individuals and different tissues.

4. The only method which will show whether this material is completely extracted from the substrate is to make a number of Abderhalden tests using a number of normal serums. Until this has been done the substrate cannot be considered fit for use with pathological serums.

THE SPECIFICITY OF CHOLESTERIN WITH SYPHILITIC SERUMS AND OF CHOLESTERIN-REINFORCED HEART ANTIGEN IN THE WASSERMANN REACTION *

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PART I

The intention of the first part of this paper is to present evidence of the safety with non-syphilitic serums and the specificity with syphilitic serums of the cholesterin heart antigen in the Wassermann reaction. The second part of the paper demonstrates that this specificity is due to cholesterin. No attempt will be made to discuss the reasons for this specificity. The work is treated largely from the technical point of view, and thus assumes a general knowledge of the principles and even of the technic of the reaction on the part of the reader.

This paper is based on one thousand Wassermann reactions which were done on the serums of eight hundred different persons, and in addition on eighty-seven Wassermann reactions on the spinal fluid of the same persons. All of these cases have been under observation in this hospital. Since, here, the Wassermann reaction is a routine laboratory test on all medical cases, about three-fifths of the cases were on the medical service under Dr. Christian's observation; likewise on the neurological division of the surgical service the Wassermann reaction is a routine test and, consequently, about one-fifth of the patients were under the observation of Dr. Cushing; the remaining fifth of this number were chiefly from the out-patient department, although a few were from the general division of the surgical service.

I shall not discuss the different antigens which have been utilized in the Wassermann reaction, but will briefly outline the development of the cholesterin antigen. Many independent observations by a great many workers[1] had shown that Wassermann "antigen" was presumably of the nature of a lipoid. Following this assumption several investigators[2] tried different lipoids, and lecithin was used most frequently.

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* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Henry A. Christian, Physician-in-Chief.

1. Lansteiner, Müller and Pötze: Wien. klin. Wchnschr., 1907, xx, 1565. Porges and Meier: Berl. klin. Wchnschr., 1908, xxi, 731. Levaditi and Yamanouchi: Compt. rend. Soc. de biol., 1907, lxiii, 740.

2. Sachs, H., and Altmann, K.: Berl. klin. Wchnschr., 1908, xxi, 494. Sachs, H. and Rondoni, P.: Ztschr. f. Immunitätsforsh., 1909, i, 132.

Browning, Cruickshank and MacKenzie[3] found that mixtures of lecithin and cholesterin gave a particularly specific reaction with syphilitic serums. The next notable advance in the preparation of antigens was the suggestion of Hans Sachs[4] to combine the alcoholic extracts of animal organs with cholesterin. The addition of cholesterin to extracts of organs was found by Sachs to endow them, however unsatisfactory alone, with properties equal to those possessed by the best syphilitic extracts. McIntosh and Fildes[5] demonstrated that an antigen prepared from human heart and cholesterin showed a notable improvement on the others, in that a much higher percentage of positive results was obtained in undoubted syphilis, while no tendency toward non-specificity was observed.

Recently, Swift and I[6] demonstrated that a 0.4 per cent. cholesterin was a safe and the optimum amount to be used. Also, we concluded that a 0.4 per cent. cholesterinized alcoholic extract of human heart made a constant and a more sensitive antigen than did a fetal syphilitic liver or a similarly made cholesterinized alcoholic extract of the heart or liver of other species, with the exception of the heart of the guinea-pig, which was apparently of the same value. Kolmer, Laubaugh, Casselman and Williams,[7] working independently of us along similar lines and at the same time very shortly afterward published their results confirming our findings.

TECHNIC

On account of the various improvements and modifications which do not enjoy universal recognition, different workers employ different technics, and consequently a certain diversity of result is inevitable. As a result of the variety of technic, the mere statement that a particular Wassermann reaction is negative is insufficient; before the value of such an observation can be appreciated, it is essential to know the methods by which it has been arrived at, and the general results which these methods usually yield. Therefore, I shall first describe my technic rather fully. All quantities of the various reagents are one-half the amounts originally described by Wassermann, Neisser and Bruck.

Complement.—Guinea-pig serum is used to supply the complement. Each day the reactions are performed, two or more guinea-pigs, after being stunned, are bled from the throat into sterile Petri dishes in

3. Browning, C. H., Cruickshank, J., and Mackenzie, I.: Biochem. Ztschr., 1910, xxv, 85; Jour. Path. and Bacteriol., 1910, xiv, 484.
4. Sachs, H.: Berl. klin. Wchnschr., 1911, iii, 2066.
5. Fildes, P., and McIntosh, J.: Brain, 1913, xxxvi, part 11.
6. Walker, I. C., and Swift, H. F.: Jour. Exper. Med., 1913, xviii, 75.
7. Kolmer, F. A., Laubaugh, E. E., Casselman, A. J., and Williams, W. W.: Practical Studies on the So-Called Syphilis "Antigens," with Special Reference to Cholesterinized Extracts, THE ARCHIVES INT. MED., 1913, xii, 660.

which the blood clots, and in the interval of one or two hours sufficient serum separates from the clot. A portion of this is made up in a 10 per cent. dilution with saline for titration.

Blood-Corpuscles. — These are obtained from the sheep at a slaughter-house, the blood being caught in a sterile bottle containing glass beads, and this bottle is shaken from three to five minutes to defibrinate the blood. This sheep blood is obtained fresh each day of the reactions, is washed four or five times with more than an equal volume of saline, the time that the centrifuge is running for the last washing is always accurately noted, and the centrifuge is always running at the same speed for this last washing each day, so that each day the amount of corpuscles is approximately the same. For the reactions 0.5 c.c. of a 5 per cent. suspension in saline is used.

Saline Solution.—Pure crystallized sodium chlorid and distilled water in the strength of 0.85 per cent. is used.

Amboceptor.—The sheep-rabbit amboceptor was used. By using diminishing quantities of the amboceptor with one unit (0.25 c.c. of a 10 per cent. dilution) of complement, 0.5 c.c. of a 5 per cent. sheep cell-suspension and saline up to the standard volume (2.5 c.c.), the minimum hemolytic dose (M. H. D.) of the amboceptor was determined. Having found that 0.0008 c.c. of this amboceptor was the M. H. D. with one unit of complement, by working with dilutions so arranged that 0.25 c.c. of the dilution contained 0.0008 c.c. of amboceptor, another dilution slightly more, and a third slightly less than this amount, it was found that 1 to 350 was the proper dilution of amboceptor (see Protocol 1). This titration was repeated with several specimens of pooled complement until a constant optimum was determined, and this optimum dilution is considered the standard. Two units of amboceptor diluted to 0.5 c.c. with saline were used to sensitize each 0.5 c.c. of the 5 per cent. sheep cell suspension for the reactions.

Standardization of the Hemolytic System.—A most important step in the Wassermann reaction is the accurate titration of the hemolytic system, and this should be done each time before performing the reactions. Occasionally sheep corpuscles are resistant to hemolysis; when such is the case I discard them and use the previous day's cells. Occasionally the complement is weaker than 10 per cent.; if so I discard it, but if it is stronger than 10 per cent., I use it in the proper strength as determined by titration. Therefore, to recapitulate, the constituents of the hemolytic system are: amboceptor made up with saline in the dilution as standardized so that 0.25 c.c. of dilution represents one unit; a sample portion of the complement made up with saline in a 10 per cent. dilution, 0.25 c.c. representing one unit; a 5 per cent. suspension of sheep corpuscles, 0.5 c.c. being the standard amount, and sufficient

saline to each tube to make the total volume the same, which should be 2.5 c.c., the volume in the Wassermann test. Both amboceptor and complement are titrated in varying amounts, and the cells, the complement and cells, and the amboceptor and cells are also controlled (see Protocol 1).

Protocol 1 shows the method of standardization of the amboceptor after the M. H. D. has been determined and diluted so that 0.25 c.c. contains one unit of amboceptor, and the protocol also represents the daily titration of the hemolytic system except that only one dilution of the amboceptor (the standardized dilution) is used. Having determined the M. H. D. of complement, the total guinea-pig serum is then diluted so that 0.5 c.c. of the dilution represents two units of complement, which amount is used in the reactions.

PROTOCOL 1.—METHOD OF STANDARDIZATION OF THE AMBOCEPTOR

Tube No.	Amount of Complement			All made up to 2.5 c.c. Incubation one hour at 37 C.	Dilution of Amboceptor *			
	Amboceptor Dilution c.c.	Guinea-Pig Serum 10 Pct., c.c.	Sheep Cells 5 Pct., c.c.		1:250	1:300	1:350	1:400
1	0.5	0.5	0.5		C. H.	C. H.	C. H.	C. H.
2	0.4	0.5	0.5		C. H.	C. H.	C. H.	C. H.
3	0.3	0.5	0.5		C. H.	C. H.	C. H.	C. H.
4	0.25	0.5	0.5		C. H.	C. H.	C. H.	C. H.
5	0.2	0.5	0.5		C. H.	C. H.	C. H.	C. H.
6	0.1	0.5	0.5		C. H.	N. C. H.	N. C. H.	Mod. H.
7	0.25	0.4	0.5		C. H.	C. H.	C. H.	C. H.
8	0.25	0.3	0.5		N. C. H.	C. H.	C. H.	C. H.
9	0.25	0.25	0.5		Mod. H.	N. C. H.	C. H.	N. C. H.
10	0.25	0.2	0.5		Sl. H.	N. C. H.	N. C. H.	Sl. H.
11	0.25	0.1	0.5		Sl. H.	Mod. H.	Mod. H.	Sl. H.
12	0.5	....	...		0			
13	....	0.5	...		0			
14	....	....	0.5		0			

* C. H. = complete hemolysis; N. C. H. = nearly complete hemolysis; Mod. H. = moderate hemolysis; Sl. H. = slight hemolysis; 0 = no hemolysis.

Human Serum.—This is inactivated at 56 C. for one-half hour and 0.1 c.c. is used in each test-tube, and 0.05 c.c. in a control-tube for natural sheep amboceptor, and 0.2 c.c. in the anticomplementary control-tube.

Preparation of Antigen.—Human heart, free from gross fat, was weighed, finely minced and placed in absolute alcohol in the proportion of 1 gm. of tissue to 10 c.c. of absolute alcohol. Extraction was carried on in the incubator at 37.5 C. for from seven to ten days, the bottles being shaken several times daily. The bottles were allowed to stand at room temperature for a day or two, and then filtered. Usually

after two or three days it was necessary to filter again, and the extract was now kept at room temperature as a stock solution. As often as necessary, 25 c.c. were taken from this stock solution and to it 0.1 gm. of cholesterin was added (a 0.4 per cent. cholesterin solution) and placed in the incubator over night, during which time the cholesterin would go into solution, but if it did not dissolve, a little shaking and a few more hours of incubation would be sufficient to dissolve it. This cholesterinized extract may be kept with safety for a month, after which time it is liable to become slightly anticomplementary, and a new portion of the stock solution should be cholesterinized.

Each day the reactions are done the antigen for the test-tubes is made as follows: to 9 c.c. of 0.85 per cent. saline is added, drop by drop with constant shaking, 1 c.c. of the 0.4 per cent. cholesterin alcoholic extract, thus making a 1:10 emulsion and 0.5 c.c. of this 1:10 emulsion of antigen is used in each test-tube.

PROTOCOL 2.—WASSERMANN REACTION

FRONT TUBES	
0.1 c.c. patient's serum.	0.1 c.c. patient's serum.
0.5 c.c. complement (2 units).	0.5 c.c. complement (2 units).
0.5 c.c. antigen No. 1 (1:10 emulsion).	0.5 c.c. antigen No. 2 (1:10 emulsion).
0.4 c.c. saline.	0.4 c.c. saline.
BACK TUBES	
0.2 c.c. patient's serum.	0.05 c.c. patient's serum.
0.5 c.c. complement.	0.25 c.c. complement (1 unit).
0.8 c.c. saline.	0.5 c.c. cells.
	1.7 c.c. saline.

Incubation one hour at 37.5 C. in water bath. Then 1 c.c. of sensitized cells is added to each tube except that one already containing cells. Incubation is again carried on for another hour in water bath at 37 C., after which time the results are noted.

In Protocol 2 the front tubes are the test-tubes and are in duplicate with the exception of different antigens; that is, the same dilution of antigen is used, but made from two different hearts and the cholesterin has been added to each heart extract at different dates. The back tubes serve as controls, the one containing 0.2 c.c. of patient's serum is the anticomplementary control. The other tube contains one-half the amount of serum and complement, no antigen and no amboceptor and the standard amount of cells; this serves as the control for natural sheep amboceptor which may be present in the serum. The reason for using two antigens and the natural sheep amboceptor control will be mentioned later. A known positive and a known negative serum are always used as controls and each antigen is controlled. Complete inhibition of hemolysis is represented by four pluses (++++),

75 per cent. inhibition by + + +, one-half inhibition by + + and less than this by a single +. These varying amounts of inhibition are determined by centrifuging, but even then there is considerable variation.

ADVANTAGES OF THIS ANTIGEN

There are three chief advantages in such an antigen; one, the ease with which it is obtained and made; another, its constant properties when made from different hearts; the third, its superior antigenic properties with syphilitic serums with no tendency toward non-specificity.

The ease of obtaining and making this antigen has been mentioned in a preceding paragraph. The alcoholic extract may be kept as a stock solution for at least six months, and to portions of this stock solution cholesterin may be added in 0.4 per cent. strength at intervals of four or five weeks, or oftener if necessary.

PROTOCOL 3.—DIFFERENCE IN ANTIGENIC—

Antigen Used	Serum of Miss W.		Serum of Mr. S.		Serum of Mr. D.	
	0.1 cc.	0.05 c.c.	0.1 cc.	0.05 c.c.	0.1 cc.	0.05 c.c.
Heart cholesterin 1:6 emulsion	++++	++++	++++	+	++++	++++
Heart cholesterin 1:12 emulsion ...	++++	+++	+	—	++++	++++
Liver cholesterin 1:6 emulsion	++++	++++	+++	—	++++	++++
Liver cholesterin 1:12 emulsion ...	+++	+	—	—	++++	++++
Liver alone 1:6 emulsion	—	—	—	—	++++	+
Liver alone 1:12 emulsion	—	—	—	—	—	—

That different hearts yield antigens of the same antigenic and anticomplementary properties has been demonstrated by McIntosh and Fildes. These workers used twenty-four different human hearts, and in addition to the above found that the addition of cholesterin rendered them invariable, so that a quantitative estimation may be carried out with different reagents and different antigens at different times with a very small margin of error. In this present work I have used ten different human hearts from patients who had died from the following causes; pneumonia, diabetic coma, uremia, general carcinomatosis, sarcoma of skull, gumma of brain and liver, carcinoma of head of the pancreas with cholemia, myxedema with chronic myocarditis, and two from syphilitic aortitis. All of these hearts had practically the same antigenic and anticomplementary properties. Furthermore, quantita-

tive estimations of their antigenic properties with different syphilitic serums and different reagents were practically the same and were always constant for the same antigen from day to day.

McIntosh and Fildes demonstrated the superior antigenic properties of the cholesterin heart antigen over other antigens with manifest syphilitic serums from primary, secondary and tertiary cases. This advantage was most apparent in syphilis of the central nervous system, including parasyphilis in which group of cases the syphilitic liver antigen has inferior antigenic properties.

Swift and I found the same advantages were apparent when we compared this antigen with those considered to be the best in use in Germany. For this work I was unable to obtain a congenital syphilitic liver, but I did make an antigen from several gummata of a liver in which the spirochetes were demonstrated, using the alcoholic extract

—Properties of Three Different Antigens

Serum of Mrs. K.		Serum of Mrs. A.		Serum of Mr. W.		Serum of Mrs. J.	
0.1 cc.	0.05 c.c.	0.1 cc.	0.05 c.c.	0.1 cc.	0.05 c.c.	0.1 cc.	0.05 c.c.
++++	++++	++++	++	++++	+++	++++	++++
++++	++++	++++	+	+++	+	++++	+
++++	+	++++	+	+++	+	++++	+
++	—	+	—	+	—	+	—
—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—

made in the same method as the heart extract. A series of Wassermanns using graded amounts of serums from known syphilitic patients was performed with the following antigens: a 0.4 per cent. cholesterinized alcoholic human heart extract, an alcoholic extract of the liver gumma and a 0.4 per cent. cholesterinized alcoholic extract of the liver gumma. Protocol 3 demonstrates the difference in antigenic properties of the three different antigens.

From the Protocol 3 it is evident that the cholesterin heart antigen is the most sensitive, the gummatous liver antigen the least sensitive — in fact, it gave no fixation with some clinically syphilitic serums — and the cholesterinized gummatous liver, although made much more sensitive by the addition of the cholesterin, was still less sensitive than the heart cholesterin antigen.

DISADVANTAGES OF THIS ANTIGEN

Careless workers and those who are untrained in and unfamiliar with the complexity and the technic of the Wassermann reaction may obtain false positive reactions in non-syphilitic cases. This can hardly be considered a disadvantage, since only trained laboratory men should do this test, and if those laboratories which do employ untrained persons — and we know such is the lamentable fact in this country and in Germany — can be stimulated to employ trained persons a noteworthy result will be accomplished, since the Wassermann reaction is one of the most, if not the most, specific laboratory test that is known at the present time.

The hemolytic system should be accurately and carefully titrated each time the reactions are done, since variations in the amount of amboceptor used cause variations in the amount of complement necessary and cholesterin binds complement, consequently too small an amount of complement may be bound partially by the cholesterin and an insufficient amount may be free to complete the hemolytic system in certain negative serums.

The cholesterinized alcoholic heart extract may become slightly anticomplementary after four or five weeks. This fact is quickly recognized by controlling the antigens without serums, and with known negative serums each time the reactions are done and by using extracts to which cholesterin has been added at different intervals.

Occasionally a certain specimen of cholesterin will be anticomplementary. Out of seven different lots of supposedly C. P. cholesterin only one lot has been anticomplementary, and this was definitely proved to be unsatisfactory. The cholesterin used in this work was purchased from Eimer and Amend and from Merck and Company, and always in small amounts in order to obtain several different samples.

NO NON-SPECIFIC FIXATION WITH NON-SYPHILITIC SERUMS

In this series of 800 different persons there were 667 who gave a negative Wassermann reaction with the 1 : 10 emulsion. In none of these cases was there a question of syphilis, and since, as previously stated, all of the cases were in patients at this hospital, they consequently were carefully observed. The diagnosis of the prominent condition in the majority of these patients is represented in the table following; those diagnoses which apply to only a very limited number of cases are grouped under miscellaneous:

Chronic cardiac disease	55	Ulcer of stomach or duodenum	8
Chronic nephritis	40	Migraine	12
Tuberculosis	30	Varicose veins	6
Cirrhosis of liver	9	Rectal abscess	5
Typhoid fever	12	Pleurisy	13
Pneumonia	25	Goiter	7
Epilepsy	18	Tonsillitis	13
Brain tumor	37	Diabetes mellitus	17
Trigeminal neuralgia	15	Tabes	4
Acromegaly	10	Neurasthenia	6
Chronic salpingitis	11	Observation	8
Malignant disease	16	Hysteria	6
Spinal cord sclerosis	8	Hernia	8
Chronic arthritis	14	Disease of eye	6
Syphilis cured	14	Cystitis and pyelitis	9
Anemia	8	Cholelithiasis	6
Skin disease	20	Normal persons	50
Metrorrhagia	6	Miscellaneous	127
		Total	667

It might be well to call attention to the few following cases in the foregoing table. The fourteen patients who gave a history of syphilis had had their chancre years ago, and following this they had very intensive treatment. In these cases the Wassermann reaction was repeatedly negative and two of the cases came to necropsy and no evidence of syphilis was made out. All of the diabetic patients had acetone and diacetic acid and large amounts of sugar in the urine when the blood was taken for the Wassermann reaction, and on several of these the reaction was repeated when they became sugar free. Three of the cases were in diabetic coma, four were in uremia and several others were *in extremis* from other causes.

In using 0.5 c.c. of the 1 : 10 emulsion of this antigen, we are taking only one-fourth of the anticomplementary dose, which is well within the limit of safety, since most workers state that one-third of the anticomplementary dose is safe. Now, this same antigen made up in a 1 : 6 emulsion and using 0.5 c.c. for each test is nearly twice as strong as the 1 : 10 emulsion, and is too near for safety to the anticomplementary dose. Nevertheless, in order to determine how near this was to the non-specific fixation limit, in 400 different serums, 0.5 c.c. of 1 : 6 emulsion was employed in an extra test-tube. These 400 cases were in two series, one of 186 consecutive serums, and the other of 214 consecutive serums. Of these 400 cases, all of which gave a negative reaction with the 1 : 10 emulsion, 380 also gave a negative reaction with the 1 : 6 emulsion. Of the 20 cases which were not entirely negative, 12 gave a questionable reaction, that is, very slight inhibition of hemolysis; on centrifuging the tubes a very few cells were evident; 8 serums gave a + + reaction, that is, 50 per cent. or less inhibition of hemolysis. The 12 cases giving such a very slight degree of inhibition may be safely set aside, since no consequence would be attached to such a

slight degree of inhibition, and mechanical errors could easily account for such. Therefore in only 8 cases, or 2 per cent., which gave a ++ reaction could any one be suspicious of non-specific fixation, and even then such reactions are always considered as negative unless the particular case is understood.

Another test-tube containing 0.2 c.c. of patients serum was used with the 1:10 emulsion in 400 consecutive cases. In none of these cases was there the slightest inhibition of hemolysis with the 0.2 c.c. of serums when there was none with the 0.1 c.c. of serums.

Therefore, in such a large series of cases, since the 1:10 emulsion gave no non-specific fixation with either 0.1 c.c. or 0.2 c.c. of serum, and since the 1:6 emulsion, which is theoretically too near the anticomplementary dose, gave only 2 per cent. non-specific fixation (and this indeed was only slight in amount) it would seem that the 1:10 emulsion of this antigen with 0.1 c.c. of serum was certainly safe and sane.

Among the 87 different spinal fluids tested, 74 were negative, and in these the cell-count did not exceed 5 per cubic millimeter, and the globulin reaction was negative with the exception of four cases of tuberculous meningitis, the diagnosis of which was verified at necropsy. The majority of the patients in these negative cases were operated on by Dr. Cushing and no syphilitic process was evident; many of the others were from cases of coma, uremia, etc. In addition to those above mentioned, there were several ventricular fluids and brain-cyst fluids obtained from operations by Dr. Cushing, all of which were negative. With many of these the 1:6 emulsion of the antigen was also used with the same negative results as with the standard 1:10 emulsion. The technic of the spinal fluid Wassermann differed from that of the serum Wassermann in that larger quantities of spinal fluid were used and the amounts were graded. Seven tubes were used for each spinal fluid; each of six tubes containing, respectively, 0.5 c.c., 0.4 c.c., 0.3 c.c., 0.2 c.c., 0.1 c.c., 0.05 c.c. and a control-tube containing 1.0 c.c. for anticomplementary control; to the six tubes with diminishing amounts of fluid were added 0.5 c.c. of the 1:10 emulsion of the antigen, 0.5 c.c. complement, and saline sufficient to make all tube contents equal, and after one hour incubation, 1 c.c. of sensitized cells was added and incubation was carried on for another hour. By using this graded system considerable information was derived concerning prognosis, diagnosis and result of treatment.

FIXATION WITH SYPHILITIC SERUMS

I am aware of the fact that the diagnosis of syphilis on the strength of a positive Wassermann reaction without any history of infection is

open to much criticism. Although I believe that a positive Wassermann reaction, properly done, with or without a history of infection, does mean syphilis (barring certain conditions, as florid scarlatina and leprosy, none of which should be clinically confused with syphilis), nevertheless, for the benefit of a doubt in the mind of the reader, the facts in support of the diagnosis of syphilis apart from a positive test will be given in some detail. Improvement clinically and symptomatically and a decrease in the intensity of the reaction under intravenous salvarsan and intramuscular mercury treatment will be considered important evidence in favor of a syphilitic process. Realizing that the burden of the proof "that this cholesterin heart antigen gives no non-specific fixation" lies in the proof that all the positive reactions were of a syphilitic nature compels me to go into considerable detail in some cases, and I trust that the reader who may not be skeptical will be patient.

Those serums which gave a positive Wassermann with the 1 : 10 emulsion of the antigen were subjected to a titration for their "fixing unit." By "fixing unit" is meant the smallest amount of serum which would give complete inhibition of hemolysis in the presence of the standard amount of complement, antigen and required saline. This quantitative test was performed as follows: The maximum quantity of serum used was 0.1 c.c., and this quantity was halved five times, so that in a series of six tubes there was respectively 0.1 c.c., 0.05 c.c., 0.025 c.c., 0.012 c.c., 0.006 c.c. and 0.003 c.c. in the various tubes; therefore, the amount of serum was varied, but the amount of complement and antigen was kept constant. If it was found that 0.012 c.c. gave complete inhibition, but 0.006 c.c. did not, then 0.012 c.c. was the "fixing unit," and from now on the capitals F. U. will represent "fixing unit."

In this series of 800 cases, there were 110 persons who gave complete inhibition of hemolysis with the 1 : 10 emulsion of the antigen. Of this number, 39 gave a definite history of a chancre which was followed by medication. These 39 cases will be dismissed with no further comment, since the chancre suffices to explain the positive Wassermann. The remaining 71 cases are tabulated below, with the diagnosis of the existing condition, and confirmatory evidence if present will be given in each case; these gave no history of chancre.

It would seem that the above-mentioned cases showed sufficient evidence to substantiate the probability of a syphilitic infection, and that the small amount of serum (F. U.) required to give complete inhibition of hemolysis was, in doubtful cases, too small to think of non-specific fixation; furthermore, the symptoms in so many of the cases which might possibly be questioned were relieved by salvarsan injections. Although the fact is not mentioned above, the "fixing unit"

No. of Cases	Diagnosis	
6	Rash	All relieved by salvarsan intravenously.
3	Tabes dorsalis	All had positive Wassermann, positive globulin, increased cell-count in spinal fluid.
2	General paresis	Same as for tabes.
7	Aneurysm	Substantiated by Roentgen-ray.
4	Dilated aorta	One patient had had six miscarriages; one had one miscarriage and two monoplegias; one had positive Wassermann elsewhere; one showed symptomatic improvement with potassium iodid medication. All were substantiated by Roentgen-ray.
5	Periostitis	Symptoms and signs disappeared after many intramuscular injections of salicylate of mercury. All verified by Roentgen-ray.
4	Gummata	Two verified by operation and all disappeared under treatment.
1	Cerebrospinal Syphilis	Wassermann and globulin positive, cells increased in spinal fluid.
5	Congenital syphilis	Definite stigmata.
4	Ulcers	All were healed by intramuscular mercury and by salvarsan.
3	Aortitis	Physical signs of; the wife of one man had two still-born and no living children.
8	Uterine *	One with two miscarriages and no children; one with three still borns and no children; one with three miscarriages and no children; one with five miscarriages and no children; one with three miscarriages and husband had positive Wassermann; one with two still borns at seventh month and no children; two with one miscarriage, several D. and C. operations and no children.
2	Dementia	Positive Wassermanns elsewhere, and repeatedly positive here.
4	Vomiting	All four had attacks of recurrent vomiting, and dizziness and all were relieved immediately by intravenous salvarsan.
2	Vertigo	Vertigo and headaches for year or more, relieved by several salvarsan injections.
1	Paroxysmal hemoglobinuria	Relieved by salvarsan. Ninety per cent. of these cases are syphilitic.
1	Laryngitis	Cured by treatment with mercury.
1	Epilepsy	Attacks stopped after salvarsan.
1	Neuralgia	Relieved by salvarsan; patient gave indefinite history of infection.
1	Pellagra	Relieved by salvarsan and Wassermann became negative after ten intravenous treatments.
1	Diabetes insipidus	
1	Pelvic disease	Admitted exposure for three years, salvarsan relieved symptoms and Wassermann became negative after several salvarsans.
2	Pneumonia	One a woman who never had borne children and the Wassermann was repeatedly positive. F. U., 0.003 c.c. One, a man, whose wife never had borne children, Wassermann repeatedly positive. F. U., 0.025 c.c.
1	Alcoholic	Wassermann positive with syphilitic liver antigen, repeatedly positive here. F. U., 0.05 c.c.
1	Diabetes mellitus	One miscarriage followed by no healthy children. F. U. 0.003++. Wassermann also positive with syphilitic liver antigen.

* Whitehouse[8] recognizes a syphilitic fibrosis of the uterus, a chronic metritis and fibrosis, with a positive Wassermann in the serum.

8. Whitehouse, B.: Jour. Obset. and Gyn. Brit. Emp., 1914, xxv, 1.

in all of the questionable cases was greatly increased by treatment, so that every two weeks, when the titration test was done, the amount of serum necessary to give complete inhibition increased.

There were twenty-four persons whose serums gave only from 50 per cent. to 75 per cent. inhibition of hemolysis with the 1 : 10 emulsion of the antigens. It is in these cases with a more or less doubtful reaction that the non-specific fixation must be ruled out.

No. of Cases	Diagnosis	
3	Tabes dorsalis	The spinal fluids of all gave a positive Wassermann and globulin and an increase in the cells. Also classical signs.
1	Congenital syphilis	Had had mercury and KI constantly for several years.
6	Tertiary	All had definite chancre followed by intensive treatment.
1	Cerebral	Spinal fluid Wassermann and globulin positive, increase in cells.
1	Secondary syphilis	Had had intensive treatment, came to hospital for salvarsan.
1	Epilepsy	Attacks relieved by potassium iodid.
1	Migraine	Relieved by intramuscular mercury and potassium iodid.
6	Miscarriage	One a woman who had two miscarriages and two still borns; one a woman who had two miscarriages and a congenital child; one a woman who had three miscarriages since a healthy child; one woman who had one miscarriage; one a woman who had seven miscarriages; one a woman who had four miscarriages and two stillborns. All the above cases became negative after intramuscular mercury injections.
1	Cerebral	Had two attacks of monoplegia with aphasia.
1	Salpingitis	Became negative after many intramuscular mercury injections.
1	?	Was diagnosed syphilitic at another hospital.
1	Catarrhal jaundice	No evidence of syphilis and became negative after jaundice cleared.

Although it is a rule that partial inhibition like that in the cases mentioned above should be considered negative or, at the most, only suspicious unless the previous condition of the patient is sufficiently well understood, it would seem that with this antigen a 50 per cent. or 75 per cent. inhibition of hemolysis really meant a pretty definite syphilitic trace. All the above-mentioned cases were repeated at least once and the degree of inhibition varied only slightly, with the exception of the catarrhal jaundice case.

There were thirteen cases with a positive Wassermann in the spinal fluid, and in all the globulin was positive and the cells increased above ten. The diagnosis in these cases was clinically certain.

THE USE OF THE 1:6 EMULSION IN CERTAIN CASES

As previously stated, the 1 : 10 emulsion is used for diagnosis and the 1 : 6 emulsion was used merely to determine in how many cases it might give non-specific fixations. The use of this 1 : 6 emulsion brought out several interesting facts. One fact noted was that several secondary syphilitic cases, when treated until their serums gave a negative reaction with the 1 : 10 emulsion, but still showing from 50 per cent. to 75 per cent. of inhibition of hemolysis with the 1 : 6 emulsion, all became positive again with the 1 : 10 emulsion after an interval of a few weeks without treatment. On the other hand, several secondary syphilitic cases which were treated until they were negative with the 1 : 6 emulsion as well as with the 1 : 10 emulsion have not become positive again at all with either emulsion after several months without treatment. Therefore, we now do not stop treatment in early cases until the serum is negative with the 1 : 6 emulsion.

The same was true in two late stages of syphilis involving the central nervous system, in both of which the serums were negative after intensive treatment, but the spinal fluid was positive with the 1 : 10 emulsion, 0.5 + + + + and 0.4 + + + +. In both these cases, one of early tabes, the other of cerebral syphilis, intraspinal salvarsanized serum was given without other medication. These two patients gradually improved, and after many treatments their spinal fluids became negative with the 1 : 10 emulsion, but they both still had symptoms, although much improved. Treatment was still continued, and when one patient was lost track of the spinal fluid was slightly positive with the 1 : 6 emulsion (0.5 + +), and his symptoms were slight. The tabetic patient is still being treated; his spinal fluid Wassermann is 0.5 + + + and his symptoms are very slight. Since these two cases with a negative spinal fluid Wassermann with the 1 : 10 emulsion still had symptoms and a slightly positive reaction with the 1 : 6 emulsion, it would seem that in central nervous system involvement there was indication for continuance of treatment until the spinal fluid Wassermann became negative to the 1 : 6 emulsion.

In two cases of tabes, one with a Charcot knee, the other with gastric crises, the blood Wassermann was negative with the 1 : 10 emulsion, but with the 1 : 6 emulsion one serum gave a + + reaction, the other a + + + + reaction. From these two cases one would infer that fixation with the 1 : 6 emulsion should invite careful consideration of a syphilitic process.

In five persons each of whom had a chancre of from one to three weeks' duration, the serums of all were negative with the 1 : 10 emulsion, but with the 1 : 6 emulsion four gave complete inhibition, and one gave 50 per cent. inhibition of hemolysis. Here again inhibition of hemolysis with the 1 : 6 emulsion would indicate a syphilitic process.

Furthermore, it was noted that when there was present in the serum much natural sheep amboceptor, the tube with 0.2 c.c. of serum and the 1 : 10 emulsion showed complete hemolysis, and the tubes containing 0.1 c.c. of serum and the 1 : 10 emulsion showed partial hemolysis, so that a questionable reaction resulted, the 1 : 6 emulsion with 0.1 c.c. of serum showed no hemolysis. In such a case the 1 : 6 emulsion threw the evidence of the questionable reaction with the 1 : 10 emulsion toward the side of a positive reaction.

With the twenty-four serums which gave partial inhibition, as reported above, with the 1 : 10 emulsion, there was from 75 per cent. to complete inhibition with the 1 : 6 emulsion, and all except one case were pretty surely syphilitic.

Therefore, from the preceding statements, it would seem that the 1 : 6 emulsion might well be used as a sort of control over the 1 : 10 emulsion, but that its value in diagnosis should be carefully considered; its value as an index to further treatment is great.

PART II

TITRATION METHODS SHOWING THE SPECIFICITY OF CHOLESTERIN WHEN USED TO REINFORCE AN ANTIGEN IN THE WASSERMANN REACTION

As previously described, all serums with a positive Wassermann were titrated in diminishing quantities with the constant normal amount of complement and antigen and sufficient saline to equalize the volume in all tubes. This was done frequently to note the improvement by treatment. The 1 : 6 emulsion of the antigen was the strength used for this titration, since it was not affected by the presence of natural sheep amboceptor, and because it was anticipated that in very early cases the serums would give too weak a reaction with the 1 : 10 emulsion to be of any value, and especially because all cases were treated until their serums became negative to the 1 : 6 emulsion. The smallest amount of serum which gave a complete inhibition of hemolysis was called the "fixing unit" or F. U. It was noted that the serums of different untreated persons had a different F. U., and this did not seem to depend on how long the person had had his syphilis. In other words, the amount of serum necessary to give a complete inhibition of hemolysis bore no relation to the stage of the disease, and the serums of different untreated persons in the same stage of the disease showed wide variation in their F. U. These facts are demonstrated in Protocol 4.

In testing the anticomplementary and antigenic properties of these various antigens with known negative and known positive serums, it was noted that although the F. U. of the serums of different persons

in the same stage of syphilis varied, the amount of antigen necessary to fix the serums of patients in the same stage remained practically constant. This fact led to further investigation along this line with the serums of persons who could be grouped clinically and by definite histories into primary, secondary and tertiary syphilis. The basis for this classification is as follows: The primary cases were those with a definite hard chancre of from one to three weeks' duration. The secondary cases were those with a rash which followed a hard chancre four to eight weeks later, and those with mucous patches in the mouth following a primary lesion; this group of cases was substantiated by the rapidity of disappearance of signs and symptoms following one or two injections of salvarsan. The tertiary cases were those with a clinical tertiary rash which appeared many months or a few years after the primary or secondary manifestations; these cases required

PROTOCOL 4.—F. U. IN RELATION TO STAGE OF DISEASE

Name	Stage of Disease	F. U. in c.c.
Mr. A.	Tertiary rash	0.012
Mrs. A.	Tertiary rash	0.025
Mr. H.	Tertiary rash	0.05
Mr. K.	Tertiary rash	0.025
Mrs. O.	Tertiary rash	0.012
Mrs. K.	Secondary rash	0.05
Mr. P.	Secondary rash	0.1
Miss McC.	Secondary rash and mucous patches	0.006
Mr. McG.	Secondary rash	0.003
Mr. I.	Congenital	0.012
Mr. F.	Congenital	0.025

from six to eight injections of salvarsan before the rash entirely faded; also in this group were placed gummatous lesions, and large broken-down ulcers which followed, by a period of years, a definite hard chancre, or unquestionable secondary manifestations. In general, syphilis would more correctly be referred to as early and late manifestations, but the preceding classification more nearly assumes the purpose of this paper.

The method used in this work is as follows: After the F. U. of the serum was determined, this was kept constant together with the complement (2 units) and the antigen was varied; diminishing amounts of antigen were used in successive tubes or, in other words, the antigen was titrated in diminishing amount with a constant amount of serum and complement. A series of eight tubes was used and to each tube containing the F. U. of serum and 2 units of complement was added respectively 0.5 c.c., 0.4 c.c., 0.3 c.c., 0.2 c.c., 0.1 c.c.. 0.05 c.c., 0.025 c.c.

of antigen, and sufficient saline to make the volume of all tubes equal. In the last three tubes the quantity of antigen, which was too small to be accurately measured, was obtained by diluting 0.4 c.c. of the 1:6 emulsion with 2 c.c. of saline, and using 0.3 c.c., 0.15 c.c. and 0.07 c.c., respectively. After an hour incubation in the water-bath at 37.5 C., 1 c.c. of sensitized cells was added to each tube and incubation was carried on another hour, at the end of which time the results were noted. The tube containing the least amount of antigen which showed complete inhibition of hemolysis was considered the result or the F. U. of antigen necessary to bind the F. U. of serum. This end-result was read after centrifuging the tubes or after allowing them to stand over night in the ice-box. Each serum always had an anticomplementary control-tube. The results obtained with several serums from typical cases is shown in Protocol 5

From Protocol 5 it is evident, as in the preceding protocol, that the amount of serum necessary to give complete fixation has no bearing on the stage of the disease; on the other hand, there is, however, a definite relation between the amount of antigen necessary to give fixation and the stage of the disease. Those serums from patients in a certain stage of the disease required a similar definite amount of antigen which showed no variation for that particular stage, although the amount of serum varied widely. It would seem that by this method one could determine whether a syphilitic rash was an early or a late manifestation, provided the patient had had little or no treatment. Several other cases with rashes, but without a definite history of infection, were by this method grouped either as early or late manifestations and the proper grouping was confirmed later by treatment; that is, if the rash was resistant to treatment it was considered a tertiary or late rash, if it yielded readily to one or two treatments it was considered a secondary or early rash. Furthermore, one is able by this method in mildly treated or non-treated cases to get a fair idea as to whether the patient has had syphilis a few weeks, a few months or a period of years. If this should hold true in a large series of cases, it would be of more than passing interest, especially in medicolegal and insurance cases.

Another interesting point is that cases with a syphilitic dilatation of the aorta, commonly called a dilated arch, as evidenced by physical signs and by Roentgen-ray examination, required a considerable larger amount of this antigen to give complete fixation than did cases with a pronounced aneurysm of the aorta. This is in keeping with the pathology of such lesions, since dilatation of a moderate degree must precede aneurysm and the progress of the lesion from one of slight dilatation to a definite aneurysm probably requires a fairly long period of

PROTOCOL 5.—F. U. IN SEVERAL TYPICAL CASES

Name	Stage of Disease	F. U. in c.c. (++++)	
		Serum	Antigen
PRIMARY			
Mr. R.	Chancre three weeks' duration	0.1	0.5
Miss R.	Chancre one week's duration	0.1	0.5
Mr. M.	Chancre three weeks' duration	0.1	0.5
Mr. S.	Chancre three weeks' duration	0.1	0.5
SECONDARY			
Mr. McG.	Chancre two months ago, sore throat, falling out of hair, rash at present	0.003	0.3
Miss McC.	Chancre, mucous patches in mouth, rash at present	0.006	0.3
Mrs. B.	Chancre six months ago, no secondaries	0.1	0.3
Mr. Z.	Chancre, three months ago, rash one month ago	0.05	0.3
Mr. P.	Chancre, uveitis	0.1	0.3
Mrs. K.	Chancre, secondary rash	0.05	0.3
B. C. H.	Chancre, eight weeks' duration	0.1	0.3
Mr. J.	Chancre, six weeks' duration, beginning rash	0.003	0.4
LATE			
Mr. H.	Chancre four years ago, tertiary rash at present	0.05	0.05
Mr. K.	Chancre eight years ago, tertiary rash at present	0.025	0.05
Mr. P.	Chancre five years ago, tertiary rash at present and ulcer	0.025	0.025
Mr. L.	Chancre nine years ago, general glandular enlargement	0.006	0.025
Mr. G.	Chancre (?) years ago.	0.025	0.025
Mrs. S.	Chancre ten years ago, ulcers in throat at present	0.012	0.025
Miss B.	Chancre five years ago, ulcer in throat now	0.025	0.05
Mr. M.	Chancre three years ago, rash now	0.1	0.05

time; in other words, it is a slow, gradual process. Unfortunately, in none of my cases could I obtain a history of chancre, and consequently I was unable to determine how long the patient had syphilis; therefore, possibly, this would be an exception to the preceding statement that, in general, one could determine by this method whether a patient had had syphilis weeks, months or years. I feel certain, though, that it does apply to syphilic rashes. Protocol 6 represents the fixation in cases with a dilated arch and those with an aneurysm.

PROTOCOL 6.—FIXATION IN CASES WITH DILATED ARCHES AND ANEURYSMS

Name	Stage of Disease	F. U. in c.c. (++++)	
		Serum	Antigen
Miss W.	Dilated arch (Roentgen-ray)	0.006	0.4
Mr. S.	Dilated arch (Roentgen-ray)	0.1	0.4
Mr. J.	Diffuse dilatation of aorta (necropsy)	0.05	0.3
Mr. F.	Aneurysm (Roentgen-ray)	0.025	0.2
Miss G.	Aneurysm (Roentgen-ray)	0.025	0.1
Mr. S.	Aneurysm (Roentgen-ray)	0.025	0.2
Mr. M.	Aneurysm, ruptured (necropsy)	0.003	0.1
Mr. N.	Aneurysm (Roentgen-ray)	0.003	0.2
Mr. H.	Aneurysm (Roentgen-ray)	0.05	0.2
Mr. F.	Aneurysm (Roentgen-ray)	0.025	0.2

In Protocol 6 it is seen that the two cases with slight dilatation of the aorta, although their serums differed in strength, required the same amount of antigen and a large amount of antigen to give complete inhibition. The case with a considerable diffuse dilatation required a little less antigen. The six cases with outspoken aneurysm whose serums differed in strength all required a still smaller amount of antigen, and the case which ruptured on the ward required even a little less than the others. Therefore, as the stage progressed from a slight dilatation through a moderate to a typical aneurysm and finally to rupture, the amount of antigen necessary to give complete fixation diminished, although the F. U. of serum bore no relation to the state of dilatation.

Observing from the foregoing protocols that the amount of serum necessary to give complete fixation was not constant for any given condition or stage of the disease, but that the amount of antigen necessary to give this complete inhibition was apparently quite constant, it was thought to be of interest to determine whether a definite increase in the amount of serum would make a correspondingly proportionate decrease in the amount of antigen required to give complete fixation. This was found to be the case, as shown in Protocol 7.

PROTOCOL 7.—Relation Between Amounts of Serum and of Antigen Required to Give Complete Fixation

Name	Stage of Disease	F. U. in c.c.	
		Serum	Antigen
Mrs. D.	Gumma under treatment	0.05 ++++	0.2 ++++
	..... with	0.01	0.1 ++++
Mr. S.	Aneurysm ..... with	0.025 ++++	0.2 ++++
		0.1	0.05 ++++
Mr. D.	..... with	0.05 ++++	0.05 ++++
		0.1	0.025++++
Mr. N.	Aneurysm ..... with	0.003 ++++	0.02 ++++
		0.012	0.05 ++++
		0.025	0.025++++
Mr. C.	Gumma ..... with	0.025 ++++	0.05 ++++
		0.05	0.025++++

In this protocol five serums with a different F. U. were selected out of a large number to illustrate the fact that increasing the quantity of serum, proportionately decreased the amount of antigen necessary to give complete inhibition of hemolysis. In the first, third and fifth cases when the F. U. was doubled, the quantity of antigen was halved; in the fourth case the F. U. was quadrupled and the antigen quantity was quartered; in the second case the F. U. was first quadrupled and this quartered the antigen, again this amount was doubled and the amount of antigen required to give complete inhibition of hemolysis was halved. Therefore, a certain quantity of serum in each case required a definite quantity of antigen to give fixation, and there was a definite mathematical variation between antigen and serum. This was likewise true of spinal fluids. This held true in all cases up to a certain limit; that is, doubling and quadrupling the F. U. caused correspondingly diminishing amounts of antigen necessary. If the serum was sufficiently increased in the foregoing manner, however, a limit was reached at which the quantity of antigen did not decrease no matter how much serum was used.

The next step was to determine whether the preceding facts held for different strengths of the same antigen. The same serum was titrated for its F. U. with different strengths of the same antigen.

The cases of Protocol 8 were selected from a larger series, since they represent work done with four different heart antigens, each antigen being used in two or more definite strengths; that is, the 1:12 emulsion was one-half as strong as the 1:6 emulsion, and the 1:24 emulsion was one-fourth the strength of the 1:6 emulsion. It is evident that a definite variation in the strength of the antigen did not bear a corresponding definite variation to the quantity of serum necessary to give complete fixation. In other words, when a certain constant quantity of antigen gave a certain F. U. with a serum, a constant quantity

PROTOCOL 8.—F. U. OF SAME SERUM WITH DIFFERENT STRENGTHS OF SAME ANTIGEN

Name	Stage of Disease	Antigen No.	Emulsion	F. U. of Serum c.c.++++
Mr. J.	Gumma of liver (autopsy)	1	1:6	0.003
		1	1:12	0.012
		6	1:6	0.003
		6	1:12	0.012
Mr. A.	Tertiary rash	6	1:6	0.05
		6	1:12	0.1
Mr. H.	Tabes	1	1:6	0.003
		1	1:12	0.012
Mr. J.	Tertiary	3	1:6	0.003
		3	1:12	0.05
		3	1:24	0.05
Mrs. M.	Latent	5	1:6	0.003
		5	1:12	0.003

of one-half the strength of antigen did not correspondingly increase the amount of serum necessary to give complete fixation. There was a wide indefinite variation in the quantity of serum necessary for its F. U. when the quantity of antigen was definitely varied.

In a number of cases the serum F. U. was determined with different definite strengths of antigen as in Protocol 8, and then each F. U. of serum was kept constant and titrated with diminishing amounts of antigens of different strength, and in addition the amount of serum was definitely increased and then titrated. A few of these titrations are given in Protocol 9.

The five cases in Protocol 9 were selected from a large series to illustrate the following points. As previously shown, in determining the F. U. of a serum the amount of serum necessary to give complete

fixation with antigens of different strengths bore no definite relation to the quantity of antigen. That is, the quantity of serum, which was the F. U. with one antigen, did not always double in amount when it was the F. U. with an antigen of one-half the strength as might be expected; for instance, in the first case, Protocol 9, the F. U. of the serum was 0.05 c.c. with both strengths of antigen 1:6 and 1:12, and in the third case the F. U. of serum with 1:6 was 0.003 c.c., but with 1:12 it required four times the amount of serum, or 0.012 c.c. After the F. U. for the serum was determined, however, a definite increase in the quantity of serum caused a corresponding decrease in the quantity of antigen necessary to fix it. This point is illustrated in the first two cases in Protocol 9. Take the first case, for instance: 0.05 c.c.

PROTOCOL 9.—TITRATION OF DIFFERENT DEFINITE STRENGTH OF ANTIGENS

Mr. D. serum F. U. with No. 6 (1:6 em.) 0.05 c.c. ++++
Serum F. U. with No. 6 (1:12 em.) 0.05 c.c. ++++
0.05 c.c. serum required 0.05 c.c. of antigen 1:6 and 0.1 c.c. antigen 1:12
0.1 c.c. serum required 0.025 c.c. of antigen 1:6 and 0.05 c.c. antigen 1:12

Mr. C. serum F. U. with No. 1 (1:6 em.) 0.025 c.c. ++++
Serum F. U. with No. 1 (1:12 em.) 0.05 c.c. ++++
0.025 c.c. serum required 0.05 c.c. antigen 1:6
0.05 c.c. serum required 0.025 c.c. antigen 1:6 and 0.05 c.c. antigen 1:12
0.1 c.c. serum required 0.1 c.c. antigen 1:12

Mr. N. serum F. U. with No. 1 (1:6 em.) 0.003 c.c. ++++
Serum F. U. with No. 1 (1:12 em.) 0.012 c.c. ++++
0.003 c.c. serum required 0.2 c.c. of antigen 1:6
0.012 c.c. serum required 0.05 c.c. of antigen 1:6 and 0.1 c.c. antigen 1:12
0.025 c.c. serum required 0.025 c.c. of antigen 1:6 and 0.05 c.c. antigen 1:12
0.05 c.c. serum required 0.025 c.c. of antigen 1:6 and 0.05 c.c. antigen 1:12

Mr. McM. serum F. U. with No. 6 (1:6 em.) 0.003 c.c. ++++
Serum F. U. with No. 6 (1:12 em.) 0.003 c.c. ++++
0.003 c.c. serum required 0.025 c.c. of antigen (1:6) 0.05 c.c. (1:12) 0.1 c.c. (1:24)
0.006 c.c. serum required 0.012 c.c. of antigen (1:6) 0.025 c.c. (1:12) 0.05 c.c. (1:24)
0.012 c.c. serum required 0.012 c.c. of antigen (1:6)

Mrs. S. serum with No. 7 (1:12 em.) 0.012 c.c. ++++
0.025 c.c. serum required 0.025 c.c. antigen (1:6) 0.05 c.c. (1:12) 0.1 c.c. (1:24)

of serum required 0.05 c.c. of antigen of the strength 1:6 and twice the amount of serum, or 0.1 c.c., required one-half the amount of antigen 1:6, or 0.025 c.c.; also 0.05 c.c. of serum required 0.05 c.c. of antigen 1:6, but twice this amount or 0.1 c.c. of serum was necessary to give fixation with the same amount of antigen, 1:12, which is one-half as strong. Therefore, a definite increase in the amount of the serum caused the same definite decrease in the required amount of antigen and vice versa. The same facts were true where three different strengths of antigen were used as is shown in the last two cases of Protocol 9. When, however, as in the last two cases, this titration is carried far enough a limit is reached above which an increase in the

serum causes no corresponding decrease in the quantity of antigen necessary to fix it. Therefore, a definite amount of serum required a definite amount of antigen up to a certain limit, but an excess of serum above this limit does not influence the quantity of antigen. For instance, in the last case 0.025 c.c. of serum required 0.025 c.c. of antigen 1 : 6, and twice this amount of serum or 0.05 c.c. required the same amount of antigen 1 : 6 and did not decrease the required amount of antigen, as was the case when smaller amounts of serum were used. This is probably explained by the fact that in the last instance we are using very large amounts of serum as compared to the F. U., and the quantity of antigen is very small; the quantity of antigen is approaching infinity and naturally sooner or later, a limit of value must be reached. Therefore, from the preceding statements one must conclude that there is a definite quantitative relation between serum and antigen.

Now, let us analyze this antigen in order to determine what accounts for this definite specificity. From the preliminary titrations of the alcoholic heart extract we know that it required 1.0 c.c. of a 1 : 6 emulsion to give fixation with a positive serum, but after the addition of 0.4 per cent. of cholesterin it required only 0.05 c.c. of 1 : 6 emulsion to give fixation with the same amount of a positive serum; therefore the cholesterin must play a most important part. Different alcoholic heart extracts containing cholesterin produce, when mixed with saline, different degrees of turbidity; one emulsion may be moderately turbid, whereas another emulsion may produce a very heavy suspension. One might consider that the difference in the turbidity of emulsions could account for variation in strength of an antigen. Such is not the case. For example, Antigen 7 formed a very slight turbidity when mixed with saline, Antigen 6 formed a heavy suspension and Antigen 4 formed a moderately heavy emulsion, still when the same serum was titrated against each antigen on the same day the serum F. U. was the same for each antigen. Furthermore, each antigen was centrifuged at high speed and the supernatant fluid was used as an antigen and the F. U. of serum remained the same as before centrifuging. Therefore, the heaviness of the emulsion or the particles forming the emulsion played no part in this specificity.

The only constituent remaining in this antigen which has not been ruled out is the cholesterin, and this is present in definite quantities in all emulsions. For instance, 0.05 c.c. of the 1 : 6 emulsion contains 0.000033 gm. of cholesterin, 0.05 c.c. of the 1 : 12 contains 0.0000165 gm. and 0.05 c.c of the 1 : 24 contains 0.0000082 gm. of cholesterin. Referring, for example, to the third case, Mr. N. in the last protocol, it is seen that with the antigen 1 : 6 emulsion, 0.003 c.c. of serum was the F. U. When this F. U. of serum (0.003 c.c.) was titrated with

diminishing amounts of antigen, 1:6, it required 0.2 c.c. of this antigen to give fixation, and this 0.2 c.c. of antigen contained 0.000132 gm. of cholesterin. When four times this amount of serum (0.012 c.c.) was titrated with the same 1:6 emulsion, only 0.05 c.c. or one-fourth the amount of antigen was necessary, this 0.05 c.c. represents 0.0000033 gm. of cholesterin. Eight times the amount of serum required only one-eighth the amount of cholesterin. The same facts hold true when the 1:12 emulsion was used. Furthermore, when the same amount of serum was titrated with two different strengths of antigen (0.025 c.c. of serum titrated with 1:6 and 1:12 emulsions), the same amount of cholesterin was necessary to give fixation, although the fluid quantity of antigen was twice as much in one case as in the other. Still further, when two portions of serum, the one twice the quantity of the other, were titrated with two different strengths of antigen, the larger quantity of serum being titrated with the weaker antigen and vice versa, the fluid quantity of antigen was twice as great in the case of the larger amount of serum with the weaker antigen, still the amount of cholesterin required in both was the same. The same facts also held true when spinal fluids were titrated in the same manner.

From the above-described methods in which this problem has been attacked in many ways — and in fact no other ways are apparent to me — it would seem quite conclusive that cholesterin played a most important part in the fixation test for syphilitic serums, and from these titration methods it would seem that a definite amount of cholesterin was necessary for the fixation of a definite amount of serum and varying the amount of serum likewise varied inversely the amount of cholesterin. The serum of syphilitic patients contains a "something" for which cholesterin has a definite fixation power in the presence of complement.

SUMMARY

The material for this paper consists of 1,000 Wassermann reactions performed on the blood of 800 different persons and 87 reactions performed on the spinal fluids of as many persons. The first few pages of this paper describe in detail the technic employed in the Wassermann reaction as used here; inasmuch as different workers use different technics, the results vary, and consequently a negative reaction is meaningless unless the technic and its general results are known. The next few pages are devoted to a discussion of the antigen. An alcoholic extract of human heart reinforced with 0.4 per cent. cholesterin was the antigen used, and for the reactions 1 part of this was added to 9 parts of saline, making a 1:10 emulsion; 0.5 c.c. of this emulsion was used in each test-tube. The advantages of such an antigen were: the ease with which it is made from any human heart; its constant

antigenic properties; and especially its superior antigenic properties over other antigens with syphilitic serums, this superior sensitiveness being most evident in the late manifestations of syphilis.

No disadvantages are apparent when the antigen is carefully controlled and all reagents are accurately titrated. The remainder of the first part of the paper is taken up with the results obtained, using this as an antigen in the Wassermann reaction. Among the 800 persons, the serums of 667 patients gave a negative reaction, and in none of these was there a suspicion of syphilis. There were 110 patients whose serums gave a positive reaction, that is a complete inhibition of hemolysis, and there was no evidence of a false reaction. There were twenty-four cases with whose serums a partial fixation was obtained, and in all of these there was evidence of syphilis which had been modified by treatment, with the exception of one person with acute catarrhal jaundice, and when the jaundice disappeared, the reaction became negative. In a series of 400 cases, in addition to the 1:10 emulsion which was used for routine diagnosis, a 1:6 emulsion was used. This 1:6 emulsion is too near the anticomplementary dose for safety; still there were no false complete inhibitions of hemolysis, and in only 2 per cent. of the cases was there a false incomplete fixation. Furthermore, it was found that in the early chancre stage and in cases which had been treated, this 1:6 emulsion was of great value, and it was definitely noted that all cases should be treated until their serums became negative with this 1:6 emulsion if a relapse was to be avoided.

The second part of the paper deals with original work in methods of titration. It was found that the amount of serum necessary to give fixation varied greatly in different persons, and in different persons in the same stage of the disease. On the other hand, after the required amount of serum necessary to give fixation (the F. U.) was determined, the amount of antigen remained constant for different persons in the same stage of the disease. Furthermore, by this means it could be ascertained whether a given rash was an early or a late one; the same facts were true in cases with syphilitic disease of the aorta, an aneurysm required less antigen in amount than a slight dilatation of the aorta. Having found by titration the least amount of serum required to give fixation with the standard amount of antigen, and then determining the least amount of antigen required to give fixation with this least amount of serum, a definite increase in the amount of serum caused a proportionate definite decrease in the amount of antigen necessary to give fixation. By elimination experiments and by substituting the actual amount of cholesterin present in each portion of antigen used, it was found that the cholesterin was the specific agent which, in the presence of complement, combined with the syphilitic serums.

CONCLUSIONS

Cholesterinized alcoholic extracts of human heart have a specific fixation property with syphilitic serums, and they do not give non-specific fixation with non-syphilitic serums, provided the reagents are accurately titrated.

The serum of syphilitic patients contains a "something" for which cholesterin has a definite fixation power in the presence of complement.

BOTULISM

A REPORT OF FOOD-POISONING APPARENTLY DUE TO EATING OF CANNED STRING BEANS, WITH PATHOLOGICAL REPORT OF A FATAL CASE *

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CLINICAL REPORT, BY DR. WILBUR

A meal of roast beef, string bean salad with mayonnaise dressing, gelatin pudding, coffee and whipped cream was partaken of by a group of young people at a sorority supper held at Stanford University on Nov. 25, 1913; twenty-four ate of the bean salad and of these twelve were taken ill within the succeeding few days with symptoms of botulism. The string beans were from two separate lots, one dark green in color, purchased at a grocery store and packed by a canning association; the others, light green in color, were put up the summer before at the home of one of the girls attending the dinner. These latter beans were apparently prepared by the process of sterilization recommended by the U. S. Department of Agriculture Bulletin, that is, boiling in the final container for one hour on three successive days. There was no food or meal taken in common by all of those poisoned except the one in question. Among those made ill was one of the waiters, who had likewise partaken of the beans. The fact that two or three of the first patients had also eaten mushrooms confused the diagnosis slightly at first. Of the twelve taken ill one died about two weeks after the meal. All of the rest had bulbar disturbances of varying degree but all made a satisfactory recovery.

The early symptoms came for the most part at the end of thirty-six to forty-eight hours and because of the eye manifestations several first consulted an eye specialist, Dr. Howard Black of Palo Alto, and he together with Dr. Thomas M. Williams were in attendance on the patients whom I had the opportunity of studying. While there was marked variability in the course and seriousness of the disease picture all were enough alike so that the description of one patient will illustrate the phenomena observed.

Girl, aged 23, Tuesday evening, Nov. 23, 1913, ate the dinner including the canned string beans of the light green color together with a little rare roast beef. The following day she felt perfectly normal except that at 10:00 in the evening the eyes felt strained after some sewing. Thursday morning,

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thirty-six hours after the meal, when the patient awoke, the eyes were out of focus, appetite was not good and she felt very tired. At night she had still no appetite, was nauseated and vomited the noon meal apparently undigested. Friday morning, two and one-half days after the meal, the eyes were worse, objects being seen double on quick movement, and it was noticed that they had a tendency to be crossed. A peculiar mistiness of vision was also complained of. She was in bed until late in the afternoon, when she visited Dr. Black. She had had some disturbance in swallowing previous to this time and stated that it felt as if "something came up from below" that interfered with deglutition. The fourth day she remained in bed, was much constipated, and noticed a marked decrease in the amount of urine voided. There was at no time pain except for occasional mild abdominal cramps, no headache, subnormal temperature, and a normal pulse. The fourth and fifth days the breathing became difficult at times and swallowing was almost impossible. The patient complained of a dry throat with annoying thirst. The sixth day there were periods of a sense of suffocation with a vague feeling of unrest and as if there might be difficulty in getting the next breath. The upper lids had begun to droop. The voice was nasal. When the attempt was made to swallow liquids they passed back through the nose. The patient felt markedly weak.

Physical examination at this time showed ptosis of both upper eyelids, dilatation of the right pupil, sluggish reaction to light of both pupils, apparent paralysis of the internal rectus of the left eye, normal retina, inability to raise the head, control apparently having been lost of the muscles of the neck, inability to swallow, absence of taste. The tongue was heavily coated and the throat was covered with a viscid whitish mucus clinging to the mucous membrane. The soft palate could be raised but was sluggish, particularly on the right side. The exudate on the right tonsil was so marked that it resembled somewhat a diphtheritic membrane. The seventh day there was some change in the condition; occasional periods occurred when swallowing was more effective, and there was less tendency to strangle. On the eleventh day there was some improvement of the eyes, still strangling on swallowing, sensation of taste was keener, and the general condition improved. The twelfth day the patient was able to move her head, but was unable to lift it except when she took hold of the braids of her hair and pulled the head forward. The eyes could be opened slightly, speech was less nasal and more distinct, and improvement in swallowing was marked. At the end of two weeks the patient was able to take soft diet freely, and at four weeks she was up in a chair for a couple of hours complaining only of general weakness and inability to use her eyes. At the end of five weeks she was able to leave the hospital and return to her home and later to resume her regular work.

The foregoing description is typical of the cases seen and corresponds to the picture of botulism, which was first clearly differentiated as a clinical entity by Van Ermengen, who, following his study of the epidemic of Ellezelles, demonstrated that the symptoms were due to a toxin formed by an anaerobic organism, the *Bacillus botulinus*. In the patients seen by me there was a wide variation in the severity of the disease, some having only transient disturbance of vision or of swallowing, others such complaints as "jaws seemed very tired," "apparent inability to chew food," "tongue seemed hard to move," "sleepy all the time," "could not walk fast," "throat filled up with mucus all the time," "tried to attend classes, legs and arms were almost powerless," "hard work climbing stairs," and "throat

felt as if there was shelf in it beyond which food could not pass but it did not hurt." The complaint of seeing double and of the mist passing over the eyes was comparatively common. The gradual onset of the symptoms and their marked variability were the most striking features. At one time a patient would show marked inability to swallow, while a little later a soft meal would be taken without difficulty. There was very little difference for some time in the severity of the clinical picture between the fatal case and some of the others. The details of these cases were reported by Dr. Thomas M. Williams at the meeting of the California State Medical Society in April, 1914.

FATAL CASE

Young healthy woman, aged 23, on the second morning following the ingestion of the meal at which time the beans were taken, complained that objects were often seen double. There was no headache or vomiting; urination apparently as usual. A laxative had been taken because of constipation and the bowels had acted. On the fourth morning the patient was unable to eat because of the inability to swallow. There was no pain. Later on in the day she swallowed with difficulty. On the sixth morning her mouth was dry, there was considerable thirst, no abdominal colic, no appetite, marked asthenia, with the muscular power in the left arm less than normal. Voice was slightly nasal with inability to articulate distinctly. Temperature was 97.8 to 99 F., pulse 104. There was ptosis of both upper lids; both pupils were dilated but reacted to light, with normal fundi. The breath was foul, tongue coated and it and the pharynx covered with sticky, whitish, viscid mucus. There was considerable edema of the uvula.

The condition did not change very much in the next few days except that the patient felt very weak, was unable to raise the head without help, at times would swallow well, at other times was unable to take the simplest food, and the pulse became more rapid and dicrotic. Blood-pressure was normal. At one time she became quite talkative and complained that her jaws did not open naturally and she could not see well but for the most part she was quiet and slightly depressed.

On the tenth day she brought up with very much difficulty some mucus which had been interfering greatly with her throat and had a period in the afternoon when she was unable to swallow, had difficulty in breathing and cold extremities. Later on she was able to take an egg-nog, but complained of a spontaneous choking sensation. In the night to the distress from these attacks was added an inability to breathe through the nose.

On the twelfth day involuntary movements of the bowels occurred. Some relief from the choking, breathless sensation was gained by swabbing the throat. The patient vomited some dark green fluid after a large, soft involuntary stool and began to feel very warm and excited, axillary temperature going up to 100.4. After a period of chills, great restlessness, choking sensation, increasing temperature and higher pulse rate together with the signs of hypostatic pneumonia, the patient had a collapse from which she recovered on the administration by Dr. Williams of an intravenous transfusion of normal salt solution. She vomited later a considerable amount of blood and although her breathing became more superficial, her weakness more evident, the sensorium remained perfectly intact.

On the thirteenth day she died following a respiratory disturbance apparently due to sudden paralysis of the diaphragm, since the heart continued to beat for some time. Various form of stimulant and other treatment were administered without avail. The necropsy, performed by Dr. William Ophüls,

was practically negative except for areas of collapse and bronchopneumonia in the posterior parts of the lungs, and certain lesions of the central nervous system, which will be described later.

SYMPTOMS AND SIGNS

When one sees a series of cases presenting such striking features as those enumerated in the two described the difficulty of making a diagnosis of botulism is not great, but it is easy to see how a sporadic case could be readily overlooked or confused with various other conditions, such as luetic bulbar paralysis, anterior poliomyelitis, etc. The symptoms noted by the various writers who have described epidemics of this type are all of the same general character.

DIGESTIVE AND SECRETORY SYSTEMS

Contrary to the usual idea of food-poisoning, there is apt to be freedom from pain except perhaps for some colic, occasional vomiting, and only at times diarrhea, in patients who have been poisoned with botulismus toxin. Obstinate constipation is the rule, the intestinal tract being paralyzed by the ingested poison. Bürger[1] reports the washing out from the stomach of food particles eaten five days previously, on the evening of the day when the infected ham was taken for breakfast. Slow absorption from this alimentary tract paralysis probably explains in part the gradual onset of the symptoms and also the finding by Kob of toxin in the blood of a child eight days after the ingestion of the infected food. Very little peristalsis was to be heard over patients seen by me except after the use of brisk cathartics and enemas. The late involuntary stools and the other gastro-intestinal features in some cases may be due to a central effect on the vagus. The first stool passed by a patient was described by Van Ermengen[2] as dark and full of mucus. Anorexia is common, and the foul breath, coated tongue, viscid, sticky, whitish mucous secretion with the generally dry mouth is accompanied apparently by a paralysis of the secretory activity of many glands (parotid enlarged at times) extending in some patients even to the lacrimal glands, so that Schumacher[3] reports the inability of a woman to shed tears when told of her husband's death. At times tears are secreted freely, and, as in one of our patients, the eyes appear watery and injected.

NERVOUS SYSTEM

The most striking effect on the nervous system is the difficulty in vision with the normal background, dilated pupils, ptosis, and

1. Bürger: Ueber zwei Gruppen von Botulismus mit zwölf Erkrankung- und fünf Todesfällen, Med. Klin., 1913, ix, 1846.
2. Van Ermengen: Ztschr. f. Hyg. u. Infectionskrankh., 1897, xxvi, 1.
3. Schumacher: München. med. Wchnschr., 1913, lx, 124.

paralysis of the various eye muscles with double vision and the disturbance in deglutition. Dizziness, sleeplessness, marked muscular weakness with no disturbance of the sensorium, no headache and no anesthesia or paresthesia are characteristic. At times various paralyses of the different skeletal muscles particularly about the neck are seen. Practically all the cranial nerves except the first and second have shown involvement in described cases; that is, ptosis, mydriasis, disturbances of accommodation (third and fourth cranial nerves), inability to cry (lacrimal nerve of the fifth cranial), dryness in the mouth (seventh and ninth cranial), disturbance of deglutition partially due to lessened secretion and partially due to nervous disturbances leading to difficulty in chewing and the muscular side of swallowing (ninth, tenth and eleventh cranial nerves), mask-like expression (seventh cranial), at times difficulty in hearing (eighth cranial), variation in speech to aphonia (twelfth), obstipation and respiratory and cardiac disturbances (tenth cranial nerve). The retention of the urine and the occasional paralyses of muscles of the limbs indicate that the spinal cord may be damaged at times. The deep reflexes are not disturbed. Romberg's and Babinski's signs both absent. No tremor and no spastic conditions have been described. We noted no angioneuroses of the skin. The sensations of the mucous membrane of the throat and mouth are dulled at times probably because of its dry condition.

CIRCULATORY AND RESPIRATORY DISTURBANCES

The temperature, pulse and respiration remain practically normal unless the vagus center is involved or a secondary infection takes place. The blood-pressure was found normal in our patients, and no abnormalities were noted in the blood itself. The feeling of compression and oppression in the chest complained of by some patients is probably nervous, not circulatory, in origin.

GENITO-URINARY SYSTEM

A lessening in the amount of practically normal urine is usually seen. At times this is due to retention. There may be paralysis of the bladder detrusors or sphincters. The small amount of urine later is perhaps due to the inability to swallow. Twenty-four hours or longer passes in some patients before urine is voided.

Throughout it must be constantly remembered that the symptoms may be extremely acute and followed by early death, or they may be gradually unfolded in their entirety, or only one or two characteristic evidences may appear.

The variations in the course of the disease may be due to the amount of toxin in the food eaten, to individual resistance or to the

amount of vascular thrombosis present. The prognosis for eventual complete recovery is good if the early part of the illness is survived. In the cases here reported only one of the twelve patients succumbed, although no early difference in the severity of the clinical picture could be seen between this patient and some of the others who recovered. Death usually occurs during the first or second week, seldom later. From 30 to 50 per cent. is a common death-rate. In the Ellezelles epidemic described by Van Ermengen only three of the thirty patients died.

DIFFERENTIAL DIAGNOSIS

The isolated case is the one that is most apt to lead to confusion in diagnosis, particularly with syphilis and poliomyelitis. When botulismus is severe enough to endanger life promptly, the disease picture is usually so distinct as to permit of ready recognition. The prominence of the paralysis of the eye muscles often brings the patient first to the ophthalmologist, who must bear in mind that conditions varying from a nystagmus to an absolute immovability of the eyeballs, always with a normal retina, may occur in botulismus. Poliomyelitis, the so-called asthenic bulbar paralysis, cerebral syphilis, the various toxic ophthalmoplegias, rabies, diphtheria, poisoning with plant alkaloids (atropin, gelsemium, hyoscyamin, etc.), methyl alcohol, and ptomains (methylguanidin, ethylendiamin, etc.) must all be ruled out before making a final diagnosis.

ANATOMICAL LESIONS, BY DR. OPHÜLS

As a result of van Ermengen's classical work the question of the pathology of botulismus appears to be well settled. The bacteriological findings have been confirmed by several later investigators and his animal experiments hardly leave any doubt as to the etiology of the disease. Although the symptoms produced in the experimental animals by means of administration of the toxin of the *Bacillus botulinus* are perhaps not absolutely identical with those observed in human beings, they are similar enough to recall the symptom-complex of the disease in man and moreover they coincide entirely with the result of intoxication of similar animals treated directly with the spoiled foodstuffs.

On the basis of the *clinical symptoms* largely one has assumed a specific action of the botulismus toxin on the ganglion cells of the central nervous system, although other effects of the poison have been observed, namely, a marked paralyzing effect on the gastro-intestinal canal and a tendency to the occurrence of multiple minute hemorrhages, more especially in pons and medulla. The former, the paralysis of stomach and bowel, might of course also be ascribed to

an affection of the motor ganglia of these organs, either centrally or peripherally.

This conception of a specific action of the toxin on the ganglion cells has been much strengthened by the histological findings in the central nervous system of animals subjected to the experimental intoxication. Van Ermengen in his original article[4] describes peculiar degenerative lesions in the ganglion cells of such animals which involve largely the Nissl granules in them, although the nucleus also appears sometimes affected. Of these changes he says:

"There are almost none in the cerebrum or in the cranial nerves, but they are very pronounced in the spinal cord, less so in medulla, in pons and in the peduncles." He adds, however: "On the whole these lesions are very variable in intensity."[5]

He also finds small perivascular hemorrhages. Marinesco,[6] who studied the same material, gives practically the same account of the alterations. He even speaks of a phagocytosis of the injured cells by neuroglial phagocytes. Kempner and Pollack[7] confirm these observations of Marinesco and of van Ermengen, but believe that in their specimens, also obtained from animals treated with the botulismus toxin, they observed a still earlier lesion of the Nissl granules, which they speak of as *klumpige Schwellung*. They did not find any evidence of phagocytosis. The question was reexamined experimentally by Ossipoff[8] in 1900. He experimented on monkeys, cats and pigs as the animals most susceptible and found lesions in the nerve-cells similar to those described by Marinesco and others. He also believes to have found evidences of phagocytosis of the damaged cells. He makes the following interesting statement:

"Within the hyperemic blood-vessels as well as on the outside of them there were found many white blood-corpuscles. In the vessels these corpuscles were sometimes bunched in masses."[9]

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4. Van Ermengen: Contribution á l'étude des intoxications alimentaires, Arch. de Pharmacodyn., 1897, iii, 213, 499.

5. "Elles sont presque nulles dans le cerveau, absentes dans les nerfs craniens et très accusés dans la moelle épinière, moins prononcées dans le bulbe, la protuberance et les pedoncles." "Ces lésions, considérées dans leur ensemble, sont très variable comme intensité."

6. Marinesco: Pathologie générale de la cellule nerveuse. Lésions sécondaires et primitives. IV. L'action du bacillus botulinus, La Presse Méd., 1897, v, 43.

7. Kempner and Pollack: Die Wirkung des Botulismustoxins (Fleischgiftes) und seines specifischen Antitoxins auf die Nervenzellen, Deutsch. med. Wchnschr., 1897, xxiii, 505.

8. Ossipoff: Influence de l'intoxication botulinique sur le système nerveux central, Ann. de l'Inst. Pasteur, 1900, xiv, 769.

9. "Dans les vaisseaux hyperemiés ainsi qu'en dehors d'eux on rencontrait aussi beaucoup de globules blancs. Dans les vaisseaux il y avait parfois une agglomération de ces globules."

The importance of this statement will become more evident in the discussion of our own findings. On the basis of the findings in the ganglion cells, Römer and Stein[10] attempted to localize more exactly the paresis of accommodation observed in some of the animals experimented on and came to the conclusion that the disturbance is localized in the nucleus of the oculomotor nerve, on account of the degenerative lesions found in certain parts of the nucleus.

It is surprising how few human brains have been the object of a careful histological investigation in this disease. Van Ermengen[4] was unable to obtain any satisfactory material in his cases. Fischer,[11] who describes an outbreak of the disease due to spoiled beans, clinically came to the conclusion that the intoxication produced "central paralysis with successive elimination of certain motor nuclei in the brain stem and of the vital centers in the floor of the fourth ventricle," also that it eventually caused a descending paralysis of the motor neurons in the anterior gray columns of the spinal cord. Parts of the brains in several of his cases were sent to the Pathological Institute at Giessen for examination, but apparently no characteristic lesions were found. In the latest publication by Bürger several new post-mortem examinations on cases dead of botulism are mentioned but in *one* of the records only there is this short allusion to specific lesions in the central nervous system:

> In the cerebrum the ganglion cells are well preserved, but in the region of the oculomotorius they show commonly dust-like disintegration of the Nissl's granules and eccentric position of the nuclei.[12]

It is well to bear in mind in this connection how equivocal these finer lesions in the bodies of the ganglion cells still are. So far as I can see they are given less significance at the present time by neurologists than they were shortly after their discovery by Nissl.

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10. Römer and Stein: Experimenteller Beitrag zur Frage nach dem Sitz und Wesen der Accommodations-parese bei bakteriellen Intoxikations-Krankheiten, Arch. für Ophth. (Graefe's), 1904, lviii, 291. "Die im Verlaufe der Botulismus-Vergiftung auftretende Accommodations-parese hat ihren Sitz im Oculomotorius-Kerngebiet und ist eine durch bestimmte Komponenten des Botulismus-Toxins hervorgerufene Degeneration von Ganglienzellen im Oculomotorius-Kern."

11. Fischer: Ueber eine Massenerkrankung an Botulismus infolge Genusses verdorbener Bohnenkonserven, Ztschr. f. klin. Med., 1906, lix, 58. "Wir gewannen ferner aus den klinischen Beobachtungen den Eindruck dass es sich bei der Giftwirkung um das Auftreten zentraler Lähmungen handelt, um fortschreitende Ausschaltung der Kerne bestimmter motorischer Gehirnnerven im Gehirnstamme und der lebenswichtige Vorgänge auslösenden, automatischen Zentren im Boden der Rautengrube." "dass das Toxin vom Gehirnstamme und der Medulla allmählich absteigend die dem motorischen Apparate zugehörenden Neuronen der Vorderhörner des Rückenmarkes lähmt."

12. Bürger: "Im Grosshirn waren die Ganglienzellen gut erhalten, während sie im Oculomotoriusgebiete vielfach staubförmigen Zerfall der Nissl's Granula, excentrische Lage des Kernes usw. erkennen liessen," Med. Klin., 1913, ix, 1846.

The brain in our case was obtained within twenty-four hours in a very good state of preservation. It has been remarked by others that in botulism the tissues remain intact for an unusually long period of time, which might suggest some interference with the normal autolytic ferments.

The gross findings at necropsy were entirely negative except for a moderate hyperemia of the cerebral vessels, which was especially pronounced at the base of the brain and in the region of the fourth ventricle, where there also was found some edema. No hemorrhages could be made out with the naked eye on several sections through the brain stem. The internal organs were markedly hyperemic, which was especially noticeable in liver, kidneys and intestines. This general hyperemia has been a constant finding in all cases of human botulism and is also found in the experimental disease in animals. The dilatation of all blood-vessels was also very evident in sections from all organs examined. Typical bronchopneumonic lesions were found in the lungs, which condition probably accelerated the death of the patient.

The following is a short description of the microscopical findings in the brain:

The brain stem was sectioned transversely at different levels at the time of the autopsy and carefully hardened in frequently changed absolute alcohol. Numerous sections were made from all levels and special attention paid to the regions of the more important nuclei. Sections were obtained from all motor and some of the sensory nuclei on both sides. The nuclei studied were those of the oculomotorius (third), trochlearis (fourth), trigeminus (fifth), abducens (sixth), facialis (seventh), acusticus (eighth), glossopharyngeus (ninth), vagus (tenth), and hypoglossus (twelfth) nerves. The following lesions were found:

Thrombosis of the right arteria vertebralis at lower end of the medulla and extending into the arteria basilaris some distance. The middle part of the arteria basilaris is free. The anterior portion of it again is filled with thrombus. There are thrombi in a few of the pial branches of the basilar artery. Many pial veins at the base of the medulla and pons are filled with thrombi more especially on the right side and there are several thrombi in the veins of the tela chorioidea above the corpora quadrigemina and the posterior part of the third ventricle. All blood-vessels in the brain-tissue are much distended and full of blood. Both in the ventral and in the dorsal parts of the brain-stem one finds quite a few small thrombosed blood-vessels, some of which are situated near important nuclei; for instance, one such was found near the right vagus nucleus, several in the nuclei of the olives, several in the substantia ferruginea, several in the right nucleus trochlearis, several near the right nucleus of the oculomotorius and similarly several near the left nucleus oculomotorius, but somewhat further away from it. Small perivascular hemorrhages were encountered quite commonly about thrombosed veins and others. The thrombi in all places were very rich in polymorphonuclear leukocytes, but no bacteria could be demonstrated in spite of the use of various staining methods, including Weigert's modification of Gram's method. All thrombi were very rich in fibrin and contained comparatively few masses of conglutinated blood platelets.

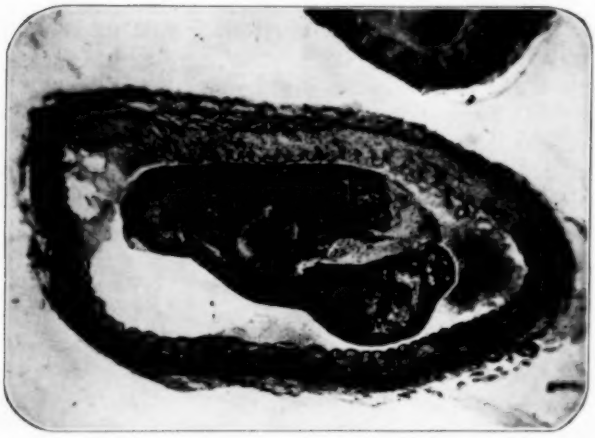

Fig. 1.—Thrombus in vertebral artery (from photomicrograph).

Fig. 2.—Thrombosis in small vein in brain tissue near oculomotor nucleus (from photomicrograph).

The Nissl granules stain unusually well in all sections especially in the large motor ganglion cells. They are quite normal in size and arrangement. Nothing unusual could be detected in spite of especially careful study of them. The nuclei of the ganglion cells are perfectly normal.

Sections were also taken from various parts of the cortex of the cerebellum. There was no difference in the appearance of the ganglion cells from these other regions. Few thrombi were seen in the pial veins. The blood-vessels in the cortex are dilated and full of blood, but none show thrombosis or perivascular hemorrhages.

No thrombi were found in any other organs in spite of the study of many sections except one in a vein in the submucosa of the intestine and the very beginning of the thrombotic process in few of the dilated vessels in the ovarian cortex.

Anaerobic cultures were made from the intestinal content both of the small and large intestines, from the cerebrospinal fluid, from the heart blood, and from the spleen. The cerebrospinal fluid and the heart blood were sterile and the *Bacillus botulinus* was not found in any of the other cultures.

I believe that on the basis of these findings it will be necessary to change considerably our ideas in regard to the action of the botulinus toxin. No evidence was found to substantiate the hypothesis of a specific action of the toxin on the nerve-cells. The negative findings in regard to any disturbance in the Nissl granules in our case are quite convincing in this regard in spite of the evidence to the contrary brought forward by other writers. The statement of Bürger[12] is so short and the lesions described in it are so slight that it hardly deserves much serious attention. But even so the fact remains that in our case the size and arrangement of the Nissl granules was quite perfect and if there should have been minor lesions they certainly were not sufficient to account for the severe clinical symptoms. So far as the positive findings in the experimental animals is concerned it may be pointed out that in them the localization of the lesions as described by Marinesco[6] and van Ermengen[4] and others does not coincide altogether with the clinical symptoms. They both emphasize the fact that the most marked involvement is found in the ganglion cells, both motor and sensory of the cord, whereas, in man at least, cord symptoms are late and rare and sensory symptoms have never been observed. The lack of histological findings in the ganglion cells does not of course prove that the poison may not have a specific action on the ganglion cells after all, but the matter remains a mere hypothesis which is greatly weakened by the positive finding of lesions which explain the clinical symptoms as well, if not more adequately.

There is present all evidence of a serious interference with the circulation in the meninges and in the brain which is most marked at the base of the brain, throughout the brain-stem where numerous hemorrhages testify to the seriousness of circulatory disturbance. Associated with this disturbance of the circulation one finds multiple

thromboses in the blood-vessels, in both the arteries and the veins. The upper part of the right vertebral artery, the posterior part of the basilar artery and again the anterior part of the same vessel are completely obstructed by thrombi. Several of the branches of these arteries in the pia are filled with thrombi. There are thrombi in many veins in the pia and in the substance of the brain, several within or in the immediate vicinity of important nuclei.

The disturbance in the blood-vessels evidently consists in an extreme vasodilatation with great slowing of the blood-current, and as such it is only part and parcel of a general paralysis of the vasculatory mechanism which has been observed and noted by all careful observers of cases of botulism. This has been usually referred to insufficient heart action. When we take into account, however, that the poison has a powerful paralyzing effect on the involuntary muscles of the gastro-intestinal tract, as is shown by the prompt paralysis of the stomach and the obstinate constipation, it would appear probable that the poison might have a similar effect on the muscular wall of the blood-vessels, either directly or indirectly through the vasomotor nerves, which would certainly have a tendency at least to contribute greatly to any interference with the circulation which, however, might be partly due to poor heart action.

Why the circulation in all cases should be especially poor at the base of the brain, more especially in pons and medulla, is not so evident. One might suggest, however, that the main blood supply to these parts through the vertebral arteries is not so abundant as the blood-supply to the cerebrum from the internal carotid arteries.

The origin of the thromboses is also somewhat puzzling. I believe the existence of them in both arteries and veins excludes the idea of embolism.

It is also somewhat difficult to explain why we should have in these cases a tendency to thrombosis so exclusively in the blood-vessels of the brain, because in other organs very little evidence of thrombosis could be detected, but even if we assumed a pretty general tendency to thrombosis those in the blood-vessels in the brain stem would provoke the most prominent symptoms on account of the crowding of so many important centers at that point.

At all events in our case the evidences of severe disturbance of circulation associated with hemorrhages and thrombosis in pons and medulla are clear and they are sufficient to explain the symptoms, whereas the assumption of specific action of the poison on certain ganglion cells, in our case, appears to be purely hypothetical.

TREATMENT

As soon as the possibility of botulism presents itself the most evident therapeutic procedure is to empty the stomach thoroughly

with a stomach tube, to wash out the large bowel and to leave in the stomach a brisk cathartic—castor oil or Epsom salts. Since the toxin is the cause of the symptoms and its absorption is slow because of the paralysis of the intestinal tract the foregoing measures should be carried out even after several days. The patient should be kept absolutely quiet, the body supplied with plenty of water, by rectum or under the skin if necessary, simple food given and great care used to prevent aspiration pneumonia. Strychnin seemed beneficial in the cases described in improving the action of the disturbed nervous centers. Other stimulants should be given as required.

The vascular conditions above described indicate the possibility of complete recovery from a condition that seems hopeless and should lend encouragement to keeping up a hard fight against the disease, even to prolonged artificial respiration in case of respiratory failure. The specific serum treatment has not been used in this country so far as I know. Leuchs[13] and others have prepared a serum which is very effective in animals. Polyvalent serums have given the best results. In Berlin this serum is prepared by the government. It is quite evident from the animal experiments that it would have to be near at hand and used promptly to be successful. That such serums should be kept in the various centers of the country is evident, as extensive botulism poisoning is apt to occur at any time.

SOURCE OF POISON

In attempting to determine the foodstuff responsible for the poisoning of the described patients each one was carefully questioned as to foods partaken of at the meal in question. As noted, there were two kinds of string beans, one dark in color from a grocery and put up by a promient canners' association, and another light green in color, domestically prepared during the previous summer. These latter beans were tender and were served as salad without preliminary heating by the Japanese cook. With mayonnaise dressing they tasted well and were eaten freely by those to whom they were served. Some of the guests were given only the dark-colored beans. None of these were taken ill. The symptoms of poisoning were so delayed that none of the bean salad was obtainable for examination but two extra cans of the same lot of home canned beans were placed at our disposal. The cans of tin were of quart size and the top was sealed with the hard red sealing wax often used for fruit jars, etc. One of these contained perfectly normal-appearing beans in a small amount of juice; the other was "blown" somewhat and its contents

13. Leuchs, J.: Ztschr. f. Hyg., 1910, lxv, 55; Kolle and Wassermann: Bacillus Botulinus (Immunität), Handbuch der Pathogenen Mikroorganismen, 1912, iv, 939 (full bibliography given).

fermented and slightly sour. Juice from both cans injected into animals had no evident toxic effects. In the fermented can Dr. R. H. Major found a long spore-bearing bacillus resembling somewhat the *Bacillus botulinus*. It was not that organism, but an unidentified one, apparently the so-called "bacillus Tourné," well known and dreaded by fruit- and catsup-canners because of the resistance of its spores to heat and its ability to spoil a pack when mixed with the raw product. Evidently the spores of the above-mentioned organism withstood the fractional sterilization of boiling of one hour on three successive days; so, while we did not find the *Bacillus botulinus* in the beans, we did find an organism which grows under similar conditions. The possibility then was present that had the beans been contaminated with *Bacillus botulinus*, that organism could have developed in one of the cans. Therefore the question of whether the string beans may provide a suitable medium is of the greatest interest in view of the present cases. The resistance of the spores of *Bacillus botulinus* to heat, (while less than that of many anaerobes), the favorable anaerobic conditions, the optimum growth at ordinary temperatures, the ability to grow either in faintly alkaline or acid mediums all favor the view that this is possible.

The famous Darmstadt epidemic was due to eating preserved bean salad served without heating. These were apparently ordinary beans (wax rather than string beans) prepared in a cooking school (Fischer[14]). Landmann[15] suggests the possibility that small contaminated meat particles were mixed with the beans but brings out no evidence in support of this idea. The characteristic butyric acid (rancid) odor and slightly sour taste makes beans used for salad particularly dangerous, since with the usual dressing a slightly sour taste is agreeable to most individuals. The destruction of the toxin by heat was well illustrated in Darmstadt by the man who came late to the celebration and thinking the beans were being served as a vegetable and not as a salad, heated them along with other food and suffered no consequences. That canned green beans may also serve as a medium for the growth of other organisms is shown by the epidemic in Leipsic in 1906 described by Rolly,[16] in which the *Bacillus coli* and *Bacillus paratyphosus B.* were later isolated from them. In California several instances of poisoning resembling botulismus have come to

14. Fischer, August: Ueber eine Massenerkrankung an Botulismus infolge Genusses "verdorbener" Bohnenkonserven (Nach Vorträgen, gehalten im ärztlichen—8/2/04—und im naturwissenschaftlichen Verein—8/3/04—in Darmstadt), Ztschr. f. klin. Med., 1906, lix, 58.

15. Landmann, G.: Ueber die Ursache der Darmstädter Bohnenvergiftung, Hyg. Rundschau, 1904, xiv, 449.

16. Rolly: Ueber Eine Massenvergiftungsepidemie mit Bohnengemüse (Bact. coli und Bact. paratyphi B), München. med. Wchnschr., 1906, liii, 1798.

our attention. Sheppard[17] describes in a graphic manner the typical and fatal poisoning of two men and a woman while on a camping trip following the eating of canned pork and beans. Peck[18] reported a similar and more extensive poisoning with eleven deaths at Sawtelle, Cal., in which he thought that canned pears were responsible.

In order to study the canned goods on which the *Bacillus botulinus* would grow, with the assistance of Drs. E. C. Dickson and E. G. Gary, a series of experiments were begun with a culture of *Bacillus botulinus* obtained from the New York Museum of Natural History by inoculating a number of cans of beans and keeping them under various conditions at various temperatures. Up to date one can tested had a slightly pungent smell and rabbits inoculated with the juice died with symptoms suggestive of botulism. The experiments will not be complete for some months, but they apparently point to string beans in sealed cans as a medium on which the *Bacillus botulinus* will grow. Further we cannot go at present. Van Ermengen[19] has carefully worked out the details of the growth of this organism, its toxin and its destruction under varying conditions, and they need not be reviewed here. The only record found of this organism occurring in nature was that of Kempner and Pollack, who found it in pigs' feces. We have as yet been unable to find out whether pigs were kept near the beans in question or whether the beans were fertilized with pigs' feces. It is fortunate that an organism with such possibilities for harm is rare.

Nevertheless the greatest care should be used in the preparation of all canned foodstuffs, particularly those kept under anaerobic conditions and apt to be eaten uncooked, to see that sufficient steam pressure and heat is used to kill all organisms and their spores. The sterilization under high pressure in vogue with all large canning companies makes their pack safe, but with the variability in domestic preparation the least rancid odor should lead to rejection of canned food and all vegetables should be reheated before being served. A long series of experiments on the penetration of heat into the interior of cans in preserving meats, etc., have been made by Bischoff and Wintgen,[20] Pfuhl,[21] Wolffhügel and Hueppe[22] and others and the need

17. Sheppard: Report of Three Cases of Fatal Ptomain Poisoning, South. California Pract., 1907, xxii, 370.

18. Peck, G. W.: South. California Pract., 1910, xxv, 121.

19. Van Ermengen: Der Bacillus Botulinus und der Botulismus, Handbuch der Pathogenen Mikroorganismen (Kolle und Wassermann) 1912, iv, 909 (with full bibliography).

20. Bischoff, H., and Wintgen, M.: Beiträge zuh Conservenfabrikation, Ztschr. f. Hyg., 1900, xxxiv, 496.

21. Pfuhl, E.: Beitrag zur bakteriologischen Untersuchung der Fleischvonserven, Ztschr. f. Hyg., 1904, xlviii, 121.

22. Wolffhügel and Hueppe: Mitt. a. d. k. Gsndhsamte, 1881, i, 395.

of steam pressure as well as heat is emphasized. Bolduan[23] describes the work of Belser and others on "blown cans" and found that a number of different bacteria more or less resistant to heat were present.

The possible relationship of epidemics to *Kalbfieber* (milk sickness) because of its similarity to botulism must be borne in mind (Crawford,[24] Schneidemühl[25]).

CONCLUSIONS

1. The twelve cases reported presented the typical clinical picture of botulism apparently due to eating of domestically prepared canned string beans served without preliminary heating. That string beans may act as a culture medium for the *Bacillus botulinus* is possible, and the possibility is being further investigated. The methods of sterilization under pressure in use by canning factories seems to preclude the possibility of the growth of *Bacillus botulinus* in their pack.

2. Vascular thromboses were found about the brain-stem in a patient dying with the symptoms of botulism. Such lesions explain better the clinical phenomena observed than does the more or less hypothetical assumption of a specific action of the botulin on certain ganglion cells.

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23. Bolduan: Food Poisoning, Treat & Co., 1909, p. 104.

24. Crawford, A. C.: The Supposed Relationship of White Snake Root to Milk Sickness or "Trembles," U. S. Dept. Agric., Bureau Plant Industry, Bull. 121, 1908, p. 5.

25. Schneidemühl: Ueber Botulismus beim Menschen und die sogenannte Geburtsparalyse bei Rindern, Centralbl. f. Bakteriol., 1898, xxiv, 577.

A NOTE ON THE NORMAL PECULIARITIES OF THE HEART-SOUNDS IN THE REGION OF THE STERNUM *

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An examination of some thirty available works on physical diagnosis and diseases of the heart reveals that none of them call attention to the fact that there is a physiological difference in the quality of the heart-sounds underneath and in the neighborhood of the sternum, as compared with the sounds over the rest of the heart.

The quality of the sounds in this situation has undoubtedly been observed frequently, but the articles bearing on the subject all assume that the peculiarity is pathological. Laennec undoubtedly heard the sound and described it in his treatise on diseases of the heart. He mistook it at first for pericardial friction, but subsequently decided that this was not the case and considered it an association of cardiac hypertrophy.

F. J. Brown described the sound in 1856 as a "chisel" sound. He also considered it a pathologic manifestation and associated it with dyspepsia.

Angel Money noted it in puerperal women in 1882 and suggested its association with friction between the two layers of the pericardium which he thought might or might not be altered in structure.

Sansom agreed as to its occurrence, but rejected Money's explanation.

Colbeck described it, in 1901, as occurring especially in connection with downward displacement of the heart in patients with emphysema. He notes, however, that it may occur under normal conditions.

Hare, in a brief note published in 1901, associates it with general debility and a feeble, irritable heart, and states that it is of frequent occurrence in the early stages of pulmonary tuberculosis.

The most careful studies of the sound have been made by Myer Solis-Cohen,[1] who describes it as a xiphosternal crunching sound. He suggests that it does not indicate a grave pathological condition, and that its association with enlargement of the heart and myocardial degeneration is to him its most significant feature.

Osler, in his brief discussion of Hare's paper, is the only observer, so far as I have been able to discover, who notes that the sound is found in the majority of healthy subjects.

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* Submitted for publication, June 9, 1914.

* From the Continuous Medical Service of the New Haven Hospital.

1. The important literature may be found in his article, "A Xiphosternal Crunching Sound," Tr. Lehigh Valley Med. Assn., 1903, Am. Jour. Med. Sc., July, 1903.

This peculiar quality of the heart-sounds underneath the sternum and in its neighborhood seems to be worthy of emphasis because the phenomenon is a normal rather than a pathological one, and because under certain conditions it may be mistaken for a pathological sound and give rise to errors in diagnosis. I have noted the almost constant presence of the sound in all sorts of cases for a number of years, and recently have studied in detail some forty cases.

The sound occurs at all ages after infancy. I am not prepared to say that it never occurs in infants, because I have not examined a sufficient number to be certain of this point, but in those which I have examined the sound was not perceptible. After the age of 2 years I have seldom failed to find it.

The quality of the sound is, to my mind, best described in the great majority of instances as a superficial scratching sound. In a few instances it has a clicking or tapping quality. The scratching quality is present with both systole and diastole. Usually it is of brief duration and of equal intensity with both sounds. Occasionally the systolic scratch is the more intense; rather more frequently the diastolic. The sound appears to be decidedly superficial, does not resemble an endocardial murmur, but does strongly suggest a friction rub. It is uninfluenced by respiration, and in many instances change of position has little or no effect on its intensity. In about 50 per cent. of the cases it is somewhat intensified by the leaning forward position or by the right or left lateral position. In the left lateral position the maximum area of the sound sometimes shifts 1 or 2 cm. to the left.

The sound is usually heard best at the lower end of the sternum opposite the fifth and sixth costal cartilages, a little to the left of the median line. I have endeavored to get an average of its distribution by marking it out on the chest in a series of patients and transferring the markings to tracing-paper. By making a composite tracing as accurately as that can be done, it is found that in the average adult the area over which the scratching quality is readily appreciable measures about 13 by 9 cm.; in children, about 7 by 8 cm. In both instances the area to the left of the median line is greater than that to the right, and shows a tendency to project downward toward the apex of the heart. In hearts which are hypertrophied or dilated from disease the area is usually distinctly enlarged, averaging about 15 by 12 cm. In a vertical direction there is a good deal of variation in the situation of the area of scratching. It is practically always prominent just above the ensiform cartilage, and occasionally can be heard below the ensiform. It only occasionally passes upward above the angle of Louis. I wish to remark, however, that there is quite a wide range of variation and that I have charted only the area of maximum intensity

of the sound because it shades off almost imperceptibly, and a certain degree of scratching quality can often be heard well beyond this area.

I am somewhat at a loss for an explanation of the sound. The writers who have regarded it as pathological have ascribed it to various known pathological lesions of the pericardium or heart, such as milk spots on the pericardium, dryness of the surface of the pericardium and ecchymoses into the subserous tissue. Others have regarded the sound as being of cardiac origin and associated with sclerosis of the coronary arteries and hypertrophy of the heart. Inasmuch as the condition is a physiological one, pathological explanations do not suffice to account for it. The sound is so much like a pericardial rub that one is tempted to assume that in spite of the presence of lubricating fluid in the pericardial sac there is still enough friction to produce sounds audible through the chest-wall. This explanation seems to me improbable, however, as in a patient with a tuberculous pericarditis with a very large effusion, I was still able to make out the scratchy quality to the heart sounds over the lower end of the sternum. A possible explanation which occurs to me is that the sound may be due to changes in the tension of the loose cellular tissue in the sternopericardial ligament which binds the anterior surface of the pericardium to the posterior thoracic wall, and which may be affected by the movements of the heart. I have no way of proving or disproving this hypothesis, nor is it one that can be readily elucidated by deadhouse findings. The location of the ligament as seen in cross-sections and at necropsy seems compatible with this explanation.

The practical importance of the scratching, substernal sound lies in the fact that it apparently becomes intensified under certain circumstances. At least this seems to me to explain certain otherwise inexplicable phenomena. Six or seven years ago, before I had given very careful attention to the sound, a patient comatose from alcohol entered my ward in the hospital, and on physical examination I very carefully described a distinct to-and-fro pericardial friction. The next morning it had entirely disappeared. Since then I have occasionally met with cases in which the scratching quality was intensified and in which I was in doubt as to whether I was dealing with a physiological phenomenon or a beginning pericarditis. These were usually patients with some acute infection associated with dilatation of the heart. On the other hand, I am sure that I have once or twice mistaken a real pericardial rub for the substernal scratching sound, and in one instance I have been able to substantiate this by necropsy. I do not believe that the sound will ever be a frequent source of error, but I am confident that it will be an occasional one. For this reason I think it important that it should be recognized as a physiological phenomenon.

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BOOK REVIEW

MODERN MEDICINE. Its Theory and Practice in Original Contributions by American and Foreign Authors. Edited by Sir William Osler, Bart., M.D., F.R.S., and Thomas McCrae, M.D. Second edition, thoroughly revised, illustrated. Lea and Febiger, Philadelphia and New York. Volume I, 1913; volume II, 1914.

The first and second volumes of "Modern Medicine" give many evidences of reediting and alteration which are sufficient to justify this new edition ot the well-known work and serve to enhance its value to the general practitioner. The contributors to these two volumes are in most instances those who prepared the articles of the first edition, though there are some changes and additions in the minor subjects, and the names of a few new authors appear in addition to the contributors to the original edition.

The arrangements of the contents of the first two volumes is in many respects different from that of the original edition. Into these two books has been condensed practically all the matter contained in the first three volumes of the old edition, and the System starts with the infectious diseases. The first volume contains sections on bacterial diseases, diseases of doubtful or unknown etiology, non-bacterial fungus infections and the mycoses. The second volume opens with the section on diseases caused by protozoa and animal parasites; then follow diseases due to physical, chemical and organic agents and diseases of metabolism; finally, the section on diseases of the respiratory system completes the volume. Not only has the sequence of the various sections been altered, but certain chapters have been entirely eliminated.

The historical survey of medicine by Sir William Osler, which formed the introduction to the original System, has been omitted.

There has been a reduction in the length of the sections which deal with the pathology of various different diseases, but discussions on diagnosis and treatment have been frequently lengthened and enlarged, so that the System should appeal particularly to the practicing physician, for whom it is most valuable. In order to obtain more space for such changes the articles on "Life-Insurance" and the chapter on "Inheritance and Disease" have been omitted. But these omissions seem justifiable since any one who wishes to study such subjects may refer to more extensive books and monographs.

In the classification of diseases there have been some noticeable changes; acute poliomyelitis is included among the bacterial diseases; pellagra is placed with the affections caused by chemical and organic agents. The chapters on typhoid fever by McCrae, those on lobar pneumonia by G. W. Norris and on tuberculosis by Baldwin, MacCallum and Brown, fill nearly half of one volume and have been so altered and revised that they are perhaps even more useful than the original articles in the first edition. The sections on the contagious diseases of childhood are well illustrated with useful plates. The chapters by Sir William Osler on syphilis give a most interesting and excellent summary of this subject so important and so difficult of study. In the treatment of this disease he emphasizes the value of the use of mercury. The diseases of metabolism are again admirably presented by Philip R. Hawk, Thomas B. Futcher, James M. Anders, George F. Still and Robert Hutchinson.

There are certain changes in the makeup of these books which have allowed of condensation of considerable reading matter in a smaller space, so that eventually the System will contain fewer volumes and be much less bulky. To do this the paper used is thinner than that originally employed, and though it is probably not so good, it makes a much lighter volume. The print, too, is large and clear. which makes the book more agreeable to read than the earlier edition.